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ANNALS OF INTERNAL MEDICINE

VOLUME 26 MARCH, 1947 NUMBER 3

THE SEPARATION OF BLOOD INTO FRACTIONS OF THERAPEUTIC VALUE*

By EDWIN J. COHN, *Boston, Massachusetts*

I. INTRODUCTION

Medicine is concerned with understanding, in the interests of control, all of the component parts of the body and their functioning. Anatomy and physiology have contributed to this understanding, as have histology, bacteriology and immunology. Alchemy has contributed both to pharmacology and to chemistry, and an unfolding chemistry has contributed a knowledge

* John Phillips Memorial Medalist Presentation to the Twenty-Seventh Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, May 14, 1946.

This work was originally supported by grants from the Rockefeller Foundation and from funds of Harvard University. It was aided early in 1941 by grants from the Committee on Medicine of the National Research Council, which included a grant from the American College of Physicians. Since August, 1941, it has been carried out under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

This paper is Number 51 in the series "Studies on Plasma Proteins" from the Harvard Medical School, Boston, Massachusetts, on products developed by the Department of Physical Chemistry from blood collected by the American Red Cross.

Our knowledge of blood has been accumulating for so many centuries that adequate references to the literature regarding each point referred to would occupy more space than this brief essay. The quotation from Mayow is from the article by T. S. Patterson, Isis, 1931, xv, 504. The quotation from Mulder is from page 101, and that from Liebig is from pages 38 and 39 of Liebig, J., Animal Chemistry, or Organic Chemistry in Its Application to Physiology and Pathology, John Owen, Cambridge, 1843. References to Mulder's early estimates of protein molecular weights and to the communication from Denis to Liebig are given in a paper on Proteins as Chemical Substances and as Biological Components in the Bulletin of the New York Academy of Medicine, 1939, xv, 639. A partial bibliography regarding blood and blood derivatives is published in Science in Progress, Yale University Press, Fourth Series, pages 319–23, 1945. Earlier chemical methods for the separation and purification of the plasma proteins were considered in Chemical Reviews, 1941, xxviii, 395, and the newer methods of plasma fractionation in ethanol-water mixtures of controlled pH, ionic strength and temperature were reported in the Journal of the American Chemical Society, 1940, lxii, 3396, and 1946, lxviii, 459. Recent studies upon separated plasma components which have led to clinical uses have been reported in the Journal of Clinical Investigation, 1944, xxiii, 417–606; 1945, xxiv, 657, 662, 671, 698, 704, 793, 802, and 1946, xxv, 304; and articles to be published shortly in the same journal; in the Journal of the American Medical Association, 1944, cxxiv, 976; 1944, cxxvi, 469, 674, 680, 944; 1945, cxxvii, 144; 1945, cxxviii, 1062, 1088; and 1945, cxxix, 270; in the Bulletin of the New York Academy of Medicine, Second Series, 1945, xxi, 202; in Surgery, 1945, xviii, 347; and in the American Journal of the Medical Sciences, 1945, ccx, 661.

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first of the elements, then of their relation to each other in the organic molecule and then of intermolecular reactions. The level of understanding, at any time, has reflected the new knowledge in the natural, as well as in the medical sciences.

Discovery of the Atmospheric Gases. The chemistry of the sixteenth and seventeenth centuries related to the blood largely through the concern of Boyle, Hooke, and Newton with the nature of the elements, especially the gases of the atmosphere. The need of air for life was recognized. Hooke noted that the movement of the lungs was merely a mechanical device for bringing air into the body and proved by experiment that an animal could be kept alive without any movement of the lungs, provided air was driven in, by a bellows, and permitted to escape by mechanical means. These brilliant early experiments in artificial respiration were supplemented by the observations of his contemporary, Mayow, "that animals exhaust the air of certain vital particles, . . . that some constituent of the air absolutely necessary to life enters the blood in the act of breathing." The vital constituent was, of course, oxygen. Mayow had thus noted the rôle in respiration of the oxygen in the air, Hooke the rôle of the lungs, Harvey of the heart, Malpighi of the capillaries, and Leeuwenhoek had noted the red blood corpuscles in the blood stream. The anatomical and physical advances in Italy and in England had by 1700 thus made possible some understanding of the mechanical bases of respiratory processes.

Development of Organic Chemistry. The observations of these natural philosophers had been appraised and organized into a system of quantitative knowledge by Lavoisier in the eighteenth century and again expanded in an exploration of the more complex organic molecules of natural systems, by Liebig and Berzelius, during the first part of the nineteenth century. The new tools that were becoming available led to Wöhler's synthesis of urea in 1828. More than a century later, although these tools had been successfully employed by Emil Fischer and his school in the synthesis of peptides from amino acids, the synthesis of the larger and more complex protein molecules, though composed of amino acids bound in peptide linkage, had not been accomplished. Meanwhile, synthetic organic chemistry had created a revolution which temporarily distracted attention from the natural products and systems of which the body is composed. The use of these tools in the exploration of the by-products of coal tar distillation and in the synthesis of simple organic molecules by Hofmann, Perkin, Baeyer, and Ehrlich preoccupied men's minds. The tradition of Paracelsus was reborn with the development of the pharmacology of unnatural products; of aspirin, phenacetin and salvarsan and, in our time, of the sulfa drugs and DDT.

Development of Descriptive Protein Chemistry. These brilliant achievements led to the temporary eclipse of observations on the natural substances of the body. The first of the amino acids to be discovered was the cystine of cystine stones described by Wollaston in 1810. Cystine was, however, not recognized as a constituent of proteins until eighty years later. Until

1865 but three amino acids had been isolated from proteins; leucine by Proust in 1819, glycine by Braconnot in 1820 and tyrosine by Liebig in 1846. Liebig had become professor of chemistry at Giessen in 1826 and the medical faculty honored him with its doctorate. A great school of protein chemists had its focus in Liebig's laboratory. In 1837 he published an "Introduction to the Analysis of Organic Bodies." Estimates were made of the great size of proteins based upon their elementary composition by Mulder, who first gave the name "protein,"—from the Greek meaning "I take the first rank" —to what he "considered as the commencement and starting-point of all other animal tissues, because these are all produced from the blood."

The British Association in 1840 acclaimed Liebig's report on "Chemistry in Its Application to Agriculture and Physiology," which was amplified in a second report to the Association in 1842, translated and published as "Animal Chemistry or Organic Chemistry in Its Application to Physiology and Pathology" by his enthusiastic contemporaries, William Gregory of King's College, Aberdeen, and John Webster of Harvard. In it Liebig wrote:

> "Two substances require especial consideration as the chief ingredients of the blood; one of these separates immediately from the blood when withdrawn from the circulation. It is well known that in this case blood coagulates, and separates into a yellowish liquid, the *serum* of the blood, and a gelatinous mass, which adheres to a rod or stick, in soft, elastic fibres, when coagulating blood is briskly stirred. This is the *fibrine* of the blood, which is identical in all its properties with muscular fibre, when the latter is purified from all foreign matters.
>
> "The second principal ingredient of the blood is contained in the serum, and gives to this liquid all the properties of the white of eggs, with which it is identical. When heated, it coagulates into a white elastic mass, and the coagulating substance is called *albumen*.
>
> "Fibrine and albumen, the chief ingredients of blood, contain, in all, seven chemical elements, among which nitrogen, phosphorus, and sulphur are found. They contain also the earth of bones. The serum retains in solution sea salt and other salts of potash and soda, in which the acids are carbonic, phosphoric, and sulphuric acids. The globules of the blood contain fibrine and albumen, along with a red coloring matter, in which iron is a constant element. Besides these, the blood contains certain fatty bodies in small quantity, which differ from ordinary fats in several of their properties."

During this time Bence-Jones carried out studies on proteins in part with Liebig, and the French physician, Denis, communicated to Liebig his observations upon blood proteins, which we now call globulins, which are soluble in neutral salt solutions; observations which he later extended and presented to the Académie des Sciences as a "Mêmoire sur le Sang Considéré quand il est Fluide, pendant qu'il se Coagule et lorsqu'il est Coagulé."

Development of Physical Chemistry. The attack on the chemistry of the proteins was not resumed with equal vigor and talent until late in the nineteenth century. Knowledge of the laws governing natural systems developed more rapidly than knowledge of the nature of the substances. Poiseuille, a French physician, deduced the laws of viscous flow because of his

interest in the capillaries of the body. Pfeffer and de Vries, two botanists, laid the foundations for our understanding of osmotic pressure as a result of their interest in the forces governing the movement of water in trees and in cells. These observations led to the concept of isotonicity and were extended by Hedin and Hamburger to the passage of water into and out of the red blood cell. All of these observations played an important rôle in the development of physical chemistry which—starting in 1878 when Van't Hoff applied the gas laws to solutions and Arrhenius, in the following year, explained the discrepant behavior of salts as due to their electrolytic dissociation into ions—has made possible understanding, first of the behavior in aqueous solution of inorganic ions and, finally, of even such complex organic ions as the proteins.

Development of Protein Physical Chemistry. Although Claude Bernard, Hoppe-Seyler and Hofmeister, among others, were concerned with the behavior of proteins and contributed technics for their preparation, the foundations for the present rich development, both in the theory and the practice of protein chemistry, were largely laid by Sir William Hardy at the turn of this century. In 1899 he supplemented earlier observations and correctly interpreted the movement of proteins in an electric field as due to their dissociation as electrolytes. Moreover, he demonstrated that their electrophoretic mobilities could vary, not only in amount but also in direction; thus demonstrating that proteins were amphoteric electrolytes.

If proteins were electrolytes it followed that protein ions were in equilibrium with the other ions of the body. If proteins were amphoteric electrolytes it followed that, though they bore positive electric charges in acid solution and negative electric charges in neutral and alkaline solutions, there would be a zone in which they bore no excess of positive or of negative charges and thus were in an isoelectric condition. Improvements in methods of characterizing proteins in terms of their electrophoretic mobilities and isoelectric points have since been made by Pauli and Michaelis, by Sørensen and Tiselius. Enzymes and hormones as well as the proteins of the blood and other tissues have been considered in these terms. Most of the proteins have been found isoelectric between pH 4.5 and 7.5 and to be far less soluble in the neutral isoelectric than in the ionic condition.

Hardy's observations extended to the interactions of isoelectric proteins and salts. In 1905 two great papers were published in the British Journal of Physiology on the serum proteins: the one by Hardy, the other by Mellanby. The interaction of proteins with salts was critically examined and the more than half century old observations of Denis on the class of serum proteins, the globulins, that are soluble in salt solutions but not in water, quantitatively formulated in terms of the concentration and the valence of the salt ions.

The further interpretation of this phenomenon had to await two advances in physical chemistry, both contributed in 1923. In that year Bjerrum offered evidence for the view that amino acids and therefore proteins, in-

stead of being uncharged molecules in the neutral condition as had previously been assumed, were dipolar ions; that is, they bore equal numbers of positive and negative charges.

There was no satisfactory approach that could be applied to our understanding of solutions of ions, dipolar ions and uncharged molecules until in 1923 Debye developed the electrochemical theory of solutions which accounts for the interaction of ions with each other as well as with organic molecules. In terms of electrostatic forces, the solvent action of salts upon globulins depends not only upon the number of electrical charges on the protein, but also upon their spatial distribution on its surface. If all of the positive and negative electric charges, which result from the amphoteric dissociation of proteins, respectively as acids and bases, are distributed symmetrically, a positive charge being surrounded by negative charges, and a negative charge being surrounded by positive charges, the interaction with inorganic ions is small. If, however, there is less electrical symmetry, so that on the average there is a larger concentration of positive electric charges at one side of the molecule and of negative electric charges at the other, the molecule has an electric moment. Though a neutral molecule cannot migrate in the electric field it orients in it, thereby increasing the dielectric constant of the solution. The interaction of proteins and electrolytes, which results in the phenomenon of the solubility of globulins in neutral salt solutions, is a function of the concentration and valence of the salt and of the electric moment of the protein.

Globulins are not the only proteins which interact with electrolytes in this way. Albumins do also. Albumins, however, are so soluble in water that their interactions with salts are observed only by measurements other than solubility or in other environments. The methods of purifying and crystallizing albumins in concentrated salt solutions, introduced in the last century by Hoppe-Seyler and Hofmeister, and perfected in this century by Sir Frederick Gowland Hopkins and S. P. L. Sørensen, obscure these relations by superimposing the non-specific mass effects of "salting-out" which apply to gases, organic molecules and other electrolytes, as well as to proteins.

Proteins may be precipitated not only by "salting-out" but also by the addition of alcohols, acetone or other water-miscible organic solvents to their solutions. Such additions at ordinary temperatures generally lead to protein denaturation. Irreversible changes in the labile protein molecule can generally be minimized, however, if the temperature is maintained sufficiently low. Sir William Hardy had observed this phenomenon during the first world war, in which his attention had been directed to the conditions for the preservation of food. Temperatures of 0° C. do not suffice, but temperatures below zero, but above the freezing point of the solution, are readily achieved in alcohol- or acetone-water mixtures. In order to investigate the interactions of albumin and neutral salts, under conditions in which the solubility of the protein was low, advantage was taken of this observation. The solubility of egg albumin was studied in 25 per cent ethanol at — 5° C.

beginning in 1932 in collaboration with my colleague, R. M. Ferry. Under these conditions denaturation was minimized. Indeed, the egg albumin, a readily denatured protein, could be recrystallized after being in 25 per cent ethanol at — 5° C. for a month if the ethanol was removed before the temperature was raised. More important from a theoretical point of view, neutral salts increased the solubility of the albumin under these conditions much as they do the solubility of globulins in water.

II. Solubility of Proteins in Alcohol-Water Mixtures of Controlled pH, Ionic Strength and Temperature

This investigation of the interaction of proteins and salts in ethanol-water mixtures at sub zero temperatures—undertaken to supplement comparable studies on amino acids and peptides of known structure, varying in electric moment and non-polar groups and thus in solubility—laid the foundation for the separations of plasma proteins that have been carried forward during this war.

The Use of Alcohol as a Protein Precipitant made possible protein fractionations at the low salt concentrations at which protein-salt interactions are maximum. This theoretical advantage has proved of great practical value in making possible the separation of proteins of closely related properties. Moreover, the small amount of salt separating with the protein precipitate rendered unnecessary the long dialysis, required to remove the large amount of salt from proteins prepared by "salting-out," before they could be injected into the body. The new conditions of fractionation in alcohol-water mixtures at low temperatures are essentially bacteriostatic. By reducing bacterial growth they have reduced the accompanying danger of pyrogenic reactions.

The Choice of a pH, close to the isoelectric point of the protein to be precipitated, and therefore close to its minimum solubility, rendered unnecessary the use of high concentrations of alcohol. Thus, 25 per cent ethanol sufficed for the precipitation of globulins of neutral isoelectric points at neutral pH, and 40 per cent ethanol for the more acid globulins and albumins at pH zones near their isoelectric points.

The Temperature was maintained close to the freezing point of the alcohol-water mixture at alcohol concentration less than 15 volumes per cent. At that and higher alcohol concentrations temperatures of — 5° C. or — 10° C. were chosen depending upon the lability and the heat of solution of the protein to be separated.

The Ionic Strength was reduced to any desired point following the initial precipitation of a protein fraction. Since euglobulins by definition are insoluble in water in the absence of salt, they separated readily at sufficiently low ionic strength, at the appropriate pH, following an initial precipitation from an alcohol-water mixture at low temperature.

Lipoproteins of different molecular size, physical and chemical characteristics and isoelectric points, and containing respectively 35 and 75 per

cent lipid, have been prepared in this way and the nature of their interactions with salt, and of the interactions holding and transporting lipid in combination with protein in aqueous solution in the blood stream, investigated.

Among Proteins with the Same Isoelectric Points differences in the influence of salt on their solubility, even at the same alcohol content and temperature, is a most effective method of achieving their separation. Specific interactions with ions which either have solvent or precipitating actions, other than those due to their ionic strength, have proved useful within the framework of this multivariable system. In the fractionation of plasma proteins that has been carried out for the Armed Forces on a large scale with the blood of roughly two and one-half million donors to the American Red Cross, a five-variable system has sufficed in which the limits were as follows:

Variable	Limits Employed		
pH	4.4	to	7.4
$\Gamma/2$	0.001	to	0.16
Ethanol concn., mole fraction	0	to	0.163
Ethanol concn., vol. % at 25°	0	to	40
Protein concn., g./liter	0.2	to	66
Temperature, ° C.	0	to	−10

These conditions have been attained, and the variables maintained constant, by the use of acetate and carbonate buffer systems to control pH and ionic strength, and by the use of ethanol as precipitant since it was readily removed by distillation. These reagents are both convenient for the processing of biological systems and safe to use in the preparation of protein and lipid products, even where large quantities are destined for intravenous use.

III. The Separation of Plasma into Fractions

Although the methods that have been developed for protein and lipoprotein fractionation are general in nature and applicable to any biological tissue, we shall, in this presentation, limit consideration to human blood. The microscope revealed, and the centrifuge facilitated, the separation of the cellular elements of the blood from the plasma. Differences in density further permit separation of the red cells from the white cells. The gross separations of the various cellular elements and the plasma is thus the first step in the dissection, first by mechanical, and then by chemical means, of this complex tissue.

The Red Blood Cells contain the respiratory protein, hemoglobin. The oxygen-combining capacity of the red cell has been treated often and completely by Barcroft, Haldane, Henderson and later workers. The complex system which is the red blood cell contains not only hemoglobin but also a large number of protein enzymes, including phosphatase, hypertensinase, cholinesterase, catalase and carbonic anhydrase. Although satisfactory evidence is not available of the value in therapy of these proteins, when separated from the cell in which they are concentrated in nature, the study of each of them should, at the least, yield further knowledge of their chemistry, their interactions and their functions.

The White Cells have been studied from the point of view of histology and bacteriology. The chemistry of their components, however, remains largely to be investigated. One enzyme, verdoperoxidase, has been shown by Agner to be present to about 1 per cent. The relation of the white cells to thromboplastic activity and to hemophilia has been suggested, but definitive chemical products concerned with these and other functions have thus far not been isolated.

The Plasma, according to Liebig, contained fibrinogen and albumin. Denis noted the salt-soluble globulins. The efforts to separate globulins further by means of this phenomenon or by "salting-out," attempted by many

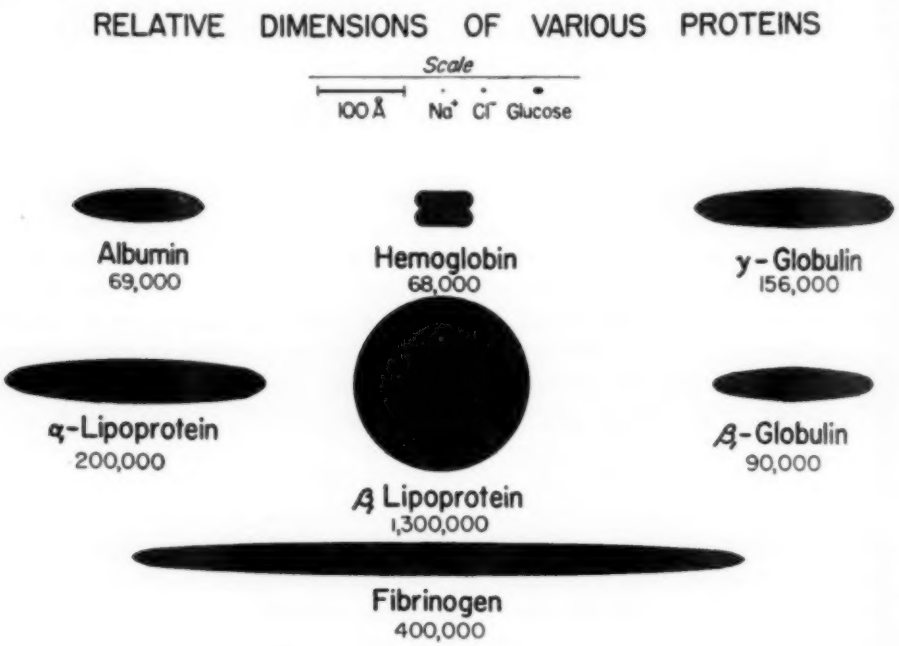

FIG. 1.

* Revised by J. L. Oncley from Figure 1, *in* COHN, E. J.: Blood and blood derivatives, Am. Scientist, 1945, xxxiii, 66.

and most critically by Sørensen, has not yielded chemical individuals. The characterization of globulins in terms of their molecular size was made possible by the ultracentrifuge developed by Svedberg. Studies in Sweden, in England, and in various laboratories in the United States carried out by means of the ultracentrifuge and other physical chemical methods, especially diffusion, viscosity and double refraction of flow, have revealed proteins of the same diameter and twice the length of albumin; still longer globulins and spherical euglobulins. All are larger than the albumins and less asymmetric than fibrinogen (figure 1).

The study of globulins in terms of their electrophoretic mobility in neutral or alkaline solution has led to the classification, due to Tiselius, of α-, β- or

γ-globulins. More recent observations have revealed in each class proteins moving with somewhat different mobilities which have been designated as α_1- and α_2-, β_1- and β_2-globulins. This classification, though useful, is also inadequate for the characterization of the diverse components of the plasma, the concentration of each of which may well be essential in maintaining a specific bodily function. Even at the present state of knowledge we recognize, in terms of other chemical or physical chemical properties, several α_1-globulins and at least four β_1-globulins.

Recognizing the very large number of components of which plasma is constituted, the chemical method for its fractionation was devised in such a way as to take advantage of differences in solubility which reflected differences in molecular size and electric charge, in non-polar side chains or in dissociated polar groups leading to different isoelectric points and electric moments. In the interest of large scale processing, plasma was first separated into as few major fractions as possible. Each fraction precipitated was then subjected to subfractionation under the conditions found most effective for the further separation and isolation of chemical components. The process that has been developed during this war, modified from time to time so as to effect the separation of all protein and lipoprotein components in as nearly their natural states as possible, yields six major fractions.

Fraction I contains most of the fibrinogen and the antihemophilic globulin.

Fraction II, obtained by subfractionation of II + III, contains the γ-globulin antibodies of proven value in the prophylaxis of measles and probably also of infectious hepatitis.

Fraction III–1 contains other antibodies, including those to typhoid O.* The isoagglutinins, including the anti-Rh antibodies of value in blood typing, are also concentrated in this fraction.

Fraction III–2 contains prothrombin and one of the components of complement. Prothrombin converted by thromboplastin to thrombin has proved of value in conjunction with fibrin foam or some other pledget as an hemostatic agent and, in conjunction with fibrinogen, in the formation of clots, films as dural substitutes and tubes for other surgical uses.

Fraction III–3 contains plasminogen, the precursor of plasmin, which has sometimes been called the fibrinolytic enzyme.

Fraction III–0 is rich in lipoprotein, including the so-called X-protein of McFarlane, which interacts in the plasma in such a way as to suggest that its molecular weight varies with concentration. The lipoproteins in this, and the next fraction listed are the bearers of cholesterol and carotene and of such steroids as estriol and vitamin A.

Fraction IV–1 is lipoprotein in nature. From the point of view of electrophoresis the lipoprotein in IV–1 is α_1-globulin, that in Fraction III–0, β_1-globulin. From the point of view of size (see figure 1), that in Fraction

* In animals many antitoxins occur in this fraction, among them those to pneumococcus and to plague.

IV–1 has been estimated to have a molecular weight of less than two hundred thousand; that in Fraction III–0 of over one million. These lipoproteins are thus totally different chemical substances which presumably serve different functions related to their structure.

Fraction IV–4 contains a variety of enzymes and hormones, including hypertensinogen and thyrotropin. It has recently been subfractionated to yield a serum esterase, a carbohydrate-rich α-globulin and the iron-binding protein, presumably responsible for the transport of iron in the plasma.

Fraction V contains the human serum albumin that has been made available in such large amounts to the Armed Forces for use in the treatment of shock, hypoproteinemia and edema. As at present released for distribution, under conditions that have been specified by G. Scatchard, L. E. Strong and W. L. Hughes, Jr., it is poor in salt and is so stable in the presence of non-polar anions, developed for this purpose largely by J. M. Luck, that it is heated in the final container for ten hours at 60° C. That these conditions suffice for the destruction of the virus of infectious hepatitis has been demonstrated by J. Stokes, Jr.

Fraction VI consists of the large amount of salts, especially citrates, and the small amount of protein left in the mother liquors following the removal of these various precipitates. It should also contain small organic molecules not bound to one or another of the proteins of plasma by specific forces. Most small molecules, for which tests have been carried out, have, however, been found in one or another of the precipitated fractions. Nonetheless, Fraction VI deserves further exploration, as do fractions of proved therapeutic value.

Distribution of the various components of plasma into these fractions is graphically represented in figure 2, which indicates accurately the proportions of the proteins separated in each fraction and suggests also the uses that have thus far been found for each.

This distribution may be considered also from the point of view of those physical chemical properties of proteins which may readily be seen to influence their functions in the body. Thus Fraction I has a very pronounced effect on viscosity due to the asymmetric fibrinogen molecules it contains, whereas Fraction V, rich in albumin, has a small effect on viscosity compared with its large effect on osmotic activity, the property which is responsible for drawing fluid into the blood stream and holding it there. Indeed, the osmotic activity of Fraction V is far greater than that of all other fractions combined. The value of the other fractions is clearly greater in conjunction with their more specific chemical properties and physiological functions.

IV. The Diversity of the Plasma Proteins

The value of blood in the prevention or treatment of disease depends but rarely upon the whole tissue. Rather it depends upon one or more of the cellular, protein or smaller organic constituents of the blood for which

there is great need. This need is for quite different constituents of the blood in hemophilia or hypertension, measles or anemia, hemorrhage or infectious hepatitis, edema, shock or hypoproteinemia.

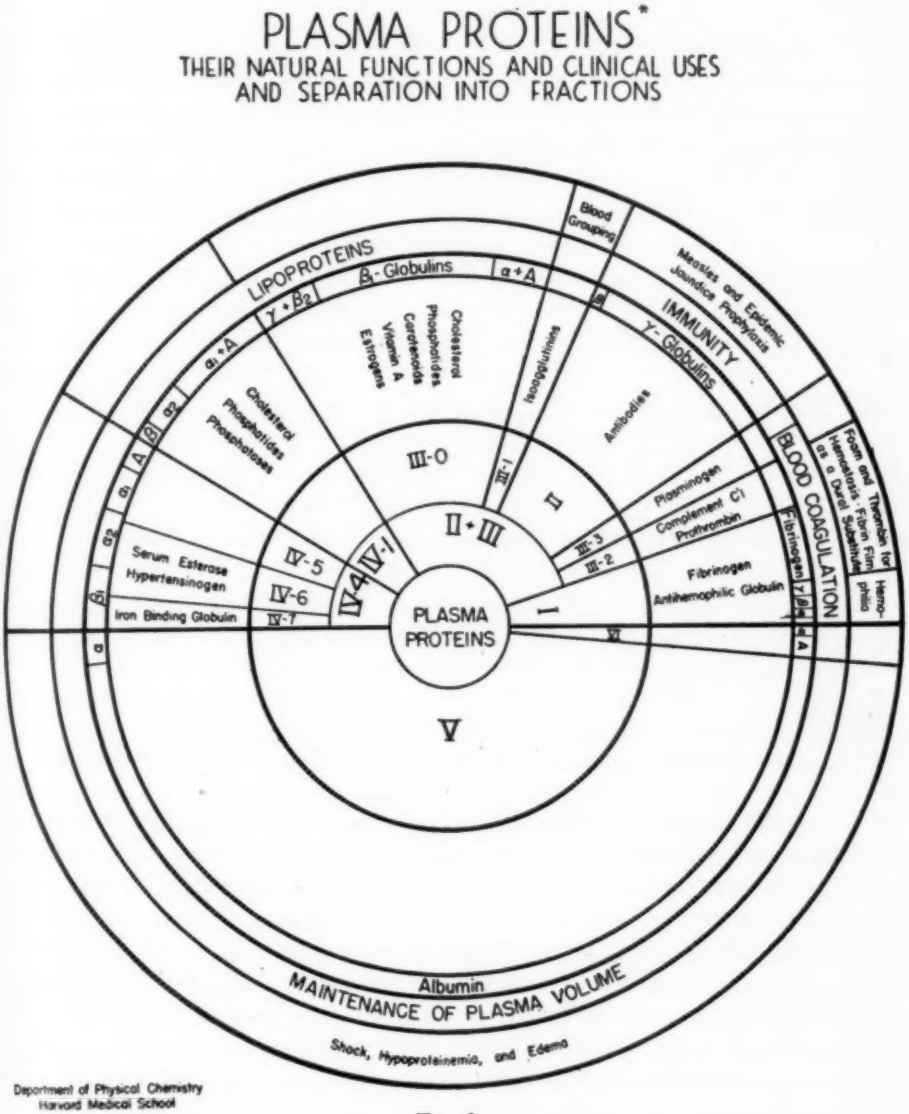

FIG. 2.

*Revised by L. E. Strong from Figure 1, *in* COHN, E. J.: Blood proteins and their therapeutic value, Science, 1945, ci, 54.

The fractionation of the plasma has made available the albumins for use in shock and the specific globulins of value in measles, hemophilia, blood typing, and blood clotting, has separated also many of the smaller molecules and

has demonstrated that they are not free in the blood stream but are in highly specific, more or less labile, combination with the larger proteins.

TABLE I

Interactions of Blood Proteins

Protein	Fraction	Interacting Molecule	Origin of Interacting Molecule	Physiological Function
Hemoglobin Carbonic Anhydrase	Red Cells Red Cells	Oxygen Carbon Dioxide	Air Tissues	Respiration
Prothrombin Fibrinogen	III-2 I	Thromboplastin Thrombin	Tissues Prothrombin	Clot Formation
γ-Globulins Complement: C'1 C'2 Isoagglutinins	II III-1 III IV III-1	Antigens	Viruses and Bacteria Red Cells	Immunity
Hypertensinogen Hypertensinase	IV-4 Red Cells and Plasma	Renin Hypertensin	Kidney Hypertensinogen	Blood Vessel Constriction
β_1-Lipoprotein α_1-Lipoprotein	III-0 IV-1	Estriol, Vitamin A Vitamin A		Lipid Transport
Choline Esterase Serum Esterase Phosphatase (Alkaline)	Red Cells IV-6 IV	Choline Esters Choline Esters* Phosphoric Acid Mono Esters		Ester Hydrolysis
Plasminogen**	III-3	Proteins	Plasma	Protein Hydrolysis
Iron Binding Serum Globulin	IV-7	Iron		Iron Transport

* Hydrolyzes Methyl Butyrate. ** Fibrinolytic Enzyme Precursor.

Thus, the accompanying table lists specific plasma globulins which have been separated which combine reversibly with iron and presumably transport it to the tissues; which dissolve water insoluble lipids, such as cholesterol, in large amounts; as well as lipid vitamins, such as vitamin A, and lipid hormones, such as estriol. Globulin enzymes with esterase and proteolytic functions have also been separated and concentrated. In other investigations albumins have been demonstrated to combine selectively with organic metal complexes such as mercurials and the sulfa drugs as well as with water insoluble organic molecules such as quinones and long chain fatty acids. The number of specific interactions between the small organic molecules and the large protein molecules that occur in the blood and in other tissues is far greater than has thus far been demonstrated. Their separation as natural protein complexes renders it possible to study the interacting physicochemical forces, as well as to explore these natural physiological mechanisms and to determine their possible value in therapy.

THE USE OF GAMMA GLOBULIN FROM LARGE POOLS OF ADULT BLOOD PLASMA IN CERTAIN INFECTIOUS DISEASES *†

By Joseph Stokes, Jr., M.D., *Philadelphia, Pennsylvania*

Although the protein fraction of blood plasma termed gamma globulin had been well defined previous to World War II, the product itself has recently assumed a greatly enhanced significance as a result of two practical developments of this war period. These are, first, the development by Dr. Edwin J. Cohn, and his co-workers at the Harvard Medical School, of a method of fractionation of plasma into several of its useful components; and, second, the pooling of plasma for fractionation from hundreds or thousands of blood donors under the system of blood collection inaugurated by the American Red Cross.

The first of these developments has served to emphasize the extraordinary diversity and essentiality of functions furnished to the body by the individual components of the blood plasma. By the method of separation of the gamma globulin fraction developed by these workers, the major portion of the antibodies in adult blood plasma against foreign protein antigens (viruses, bacteria, toxins, pollens, etc.) has been obtained. It must be emphasized that the process of fractionation of gamma globulin not only separates but also concentrates the antibodies.[1] The concentration of antibodies in the gamma globulin thus prepared is approximately 25 times that of normal pooled plasma.[2]

The second of these practical developments, namely the pooling of plasma from hundreds or thousands of adult blood donors, while only of quantitative value in the separation of such plasma components as albumin, may be, and usually is, of great qualitative value in respect to gamma globulin. The presence of antibodies against infectious diseases in human plasma appears to depend upon exposure to antigenic stimuli resulting both from subclinical or inapparent and from clinical infections.

The large size of the plasma pools developed by the American Red Cross tends to assure a surprisingly uniform titer of antibodies against the infectious agents endemic to the geographic area in which the blood donors reside. In studies of gamma globulin obtained from donors in the eastern region of the United States, Dr. Werner Henle of the Children's Hospital,

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† These investigations have been carried out as a project of the Commission on Measles and Mumps, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

We wish to express our great appreciation for the assistance of Mrs. Jeanette H. Levens and Miss Beatrice Payson without whose indispensable contributions in carrying out the technical procedures these investigations could not have been completed.

Philadelphia, found no detectable antibodies against Western equine encephalomyelitis virus, whereas antibodies against the Eastern equine encephalomyelitis virus were found in considerable amounts.[8] We are not aware of any evidence of the opposite picture in the gamma globulin obtained from Western donors, but it is probable that such a contrast would be found. Following the influenza A epidemic of November and December 1943 the gamma globulins from all areas of the United States gave evidence of a marked general increase in the antibodies against influenza A virus. A direct relationship between the height of such antibodies and individual resistance to influenza A has been demonstrated by a number of workers, including our laboratories in Philadelphia.[18] Thus the general level of donor's antibodies in any population may provide an indication of its susceptibility to the epidemic disease as well as evidence of a recent epidemic wave of influenza. The uniformity of antibody levels in pooled plasma and thus in gamma globulin depends chiefly therefore upon the following factors:

1. The presence of endemic or of recent epidemic disease in the geographical area from which the blood is drawn.
2. The amount and the duration of antibodies resulting from specific infections.
3. The number of donors contributing to the pool.

Certain of these factors can be controlled in the collection of pooled plasma.

For a discussion of gamma globulin from pooled plasma it appears important to review some theoretical considerations relating to certain of the epidemic diseases of childhood caused by viruses, and also certain data recently accumulated concerning the possible uses of gamma globulin in such diseases.

The diseases chosen for this particular comparison are: (1) Measles; (2) Mumps; (3) Infectious (epidemic) hepatitis; (4) Poliomyelitis.

Although not demonstrated conclusively in any of these four diseases it appears possible from the facts now available that either apparent or inapparent infection in childhood or early adult life with the four viruses effects a slowly developing permanent immunity to them in the greater part of the general population. Because of its ease of transmission, measles immunizes the general population earlier than the other three diseases. Infectious (epidemic) hepatitis appears to be the least readily transmissible (although it may be present at times in drinking water) of the four diseases and therefore may not immunize most of the population until the age range of approximately 30 to 35 years. Mumps and poliomyelitis would appear to occupy a position between measles and infectious hepatitis, depending upon the ease with which they are transmitted in varying aggregations of individuals. Thus, under usual conditions in the United States larger numbers of frank clinical cases of mumps and poliomyelitis occur among

young adults than is the case with measles. The rapidity with which a population is immunized also obviously depends upon whether it is urban or rural. The unusual aggregations consequent to war-time conditions accelerate the immunization of persons from rural groups. The incidence of frank clinical cases of measles, mumps, infectious hepatitis, and poliomyelitis in the entire population diminishes in the order named. This order of incidence is not theoretical; the facts are well known. In contrast to the incidence of frank clinical cases, it appears possible (a theoretical possibility supported by considerable data) that the incidence of subclinical or inapparent infections increases, rather than diminishes, in the same order, measles having very few and poliomyelitis a great number of subclinical or inapparent cases. If most of the general population throughout its early years is permanently immunized against these infections by an interaction between host and parasite, regardless of whether the interaction is apparent or inapparent, then it is highly probable that the gamma globulin obtained from the general population in an age range above 30 years would contain antibodies in concentrated amounts against all of these diseases. These theoretical considerations have been strengthened by considerable experimental evidence.

Whether or not such concentrated antibodies are present and will passively protect against measles, mumps and infectious hepatitis has been studied in humans. Although no tests have been made in man due to war conditions, considerable evidence from studies of mice, cotton rats and monkeys indicates the presence in gamma globulin from human plasma pools of large amounts of antibodies against certain strains of poliomyelitis virus.

In passing from theory to practice the results of experimental study of these four diseases now may be considered.

Measles. In measles the data have been reviewed previously by a number of workers. Studies at the Children's Hospitals in Boston [5] and Philadelphia [6] have indicated that gamma globulin represents the most satisfactory biological as yet developed for passive protection of exposed susceptibles or for attenuation of the disease. The uniformity of antibodies demonstrated against other antigens than measles virus offers considerable assurance that the globulin in general has a constant titer of measles antibodies. The variables encountered in the clinical studies have been very few and in all probability have been associated with differing exposures and with a variation in host resistance.

Conclusive evidence concerning the value of gamma globulin in the treatment of early cases of measles must still await further studies although the data thus far obtained have suggested that the disease may be modified when large doses of globulin are administered in the prodromal stage of the disease, at or previous to the appearance of Koplik spots.[6]

Mumps. That the presence of considerable amounts of specific antibodies in pooled convalescent plasma or in gamma globulin may not be sufficient to protect against certain virus diseases has been well demonstrated

in the case of mumps in the experimental monkey by Dr. John F. Enders.[7] Following intraparotid injection of a mixture of equal parts of active mumps virus suspension and convalescent human serum only partial protection against parotitis in monkeys could be demonstrated. When gamma globulin derived from plasma obtained by Lt. Colonel Aims C. McGuinness from mumps convalescent cases was used in similar neutralization tests, somewhat more effective protection in monkeys against the disease was noted. Evidence of the comparative values of ordinary gamma globulin and of gamma globulin derived from the fractionation of convalescent plasma was obtained by Captain Sydney S. Gellis and Lt. Col. Aims C. McGuinness under the Commission on Measles and Mumps, Army Epidemiological Board.[8] As obtained from their data table 1 indicates that when 20 ml. of

TABLE I

Comparison of Incidence of Orchitis in Alternate Cases of Mumps Injected with Convalescent Gamma Globulin—20 ml.—on First Day of Illness with Incidence of Orchitis in Alternate Controls

	No. Patients Who Developed Orchitis	Incidence of Orchitis (%)
No. of injected patients.....51	4	7.8
No. of controls.....51	14	27.4

gamma globulin from convalescent pools were injected parenterally in the first 24 hours after the onset of epidemic parotitis a diminution in the incidence of orchitis to 7.8 per cent occurred, while no significant effect had been obtained from the parenteral injection of 50 ml. of ordinary gamma globulin. In all large outbreaks of mumps in the U. S. Army as well as in the units studied, the incidence of orchitis has approximated 27 to 33 per cent, thus indicating that the protection afforded by the gamma globulin from convalescent plasma was apparently not a chance occurrence, but was a result of the injected material. This difference obtained in the two groups is statistically significant. The obvious conclusion is that the protective antibodies must be administered in considerable amounts to be effective. It remains to be determined whether or not the titer of complement fixing antibody which was considerably greater in the gamma globulin from convalescent plasma (Enders) is an index of the protective value of the material.

Although insufficient evidence is available, apparently gamma globulin from plasma pools derived from the general population is not usually effective in protecting exposed susceptibles against mumps in amounts up to 50 ml. Considerable amounts of complement fixing antibodies in the pooled plasma of the general adult population from whom the blood is drawn and thus in the gamma globulin emphasize the finding of Drs. J. F. Enders and L. W. Kane in Boston, together with Drs. E. P. Maris and J. Stokes, Jr., in Philadelphia [9, 10] that when an epidemic of mumps sweeps through a group of susceptibles in a children's institution, in addition to those who contract

frank clinical cases, there is also a considerable group of susceptibles who suffer inapparent or subclinical infections. The latter group develops complement fixing antibodies and positive skin tests to heated mumps virus for the first time as a result of such inapparent infections and apparently is immunized following such exposure. It is reasonable to suppose that in this manner most of the susceptibles gradually disappear throughout early life as a result of repeated exposures, whether or not they suffer from frank clinical mumps, and in a reciprocal manner, antibodies appear in the general population.

The value of gamma globulin in mumps thus appears to depend upon facilities for the pooling and fractionation of large amounts of convalescent plasma. In time of peace only moderate amounts of convalescent plasma would be available. If this could be obtained, which seems problematical, it should probably be reserved for treatment of adult males in the first 24 hours of their disease with the aim of preventing or attenuating acute orchitis. The equivalent amount of pooled convalescent plasma injected intravenously should be equally effective but is not as readily preserved as the gamma globulin due to required storage facilities and deterioration. Also the risk of producing serum hepatitis apparently is absent in the case of gamma globulin.

Infectious (Epidemic) Hepatitis. In measles and mumps, one is dealing with virus agents which can at least be studied in monkeys, if not in other animals. Such is not the case in infectious (epidemic) hepatitis, since no susceptible animal has been found. Also in measles and mumps there appear to be few differences in the antigenic properties of their respective viruses inasmuch as one attack usually confers a permanent immunity against all other epidemic strains of virus. Due to the low incidence of frank cases of infectious (epidemic) hepatitis during times of peace, adequate data concerning the antigenic relation of epidemic strains are lacking. Also the virus agent or agents responsible for homologous serum hepatitis may or may not have an antigenic relationship to infectious (epidemic) hepatitis.[11]

TABLE II

Infectious (Epidemic) Hepatitis and Homologous Serum Hepatitis Comparison

Observation	Infectious Hepatitis	Serum Hepatitis
1. Fever associated with onset	Usually exceeds 100° F.	Seldom exceeds 100° F.
2. Usual interval from exposure to jaundice	20–40 days	60–120 days
3. Secondary cases not related to injection of blood products	Common	Uncommon
4. Human biological materials known to contain causative agent	Feces and blood	Blood
5. Age susceptibility	Uncommon after 40	Apparently common after 40
6. Oral administration of infective serum	+	−
7. Homologous immunity	+	+
8. Heterologous immunity	−	−

TABLE III *

Studies on Cross Immunity Between Serum Hepatitis Virus (S.H.) and Two Strains of Infectious (Epidemic) Hepatitis Virus (I.H.Pa. and I.H.S.)

Volunteers		Challenge Inoculation		Results		
Status	No.	Virus	Route	No Hepatitis	Questionable Hepatitis	Definite Hepatitis
Previous infection with Virus S.H.	9	S.H.	Parenteral	4	5	0
	5	I.H. Pa.	Parenteral or oral	0	1	4 (80%)
Previous infection with Virus I.H. Pa.	12	I.H. Pa.	Oral	11	1	0
	5	I.H. S.	Oral	5	0	0
	4	S.H.	Parenteral	2	0	2 (50%)
Previous parenteral inoculation with Virus I.H. Pa., without subsequent apparent infection	9	I.H. Pa.	Oral	9	0	0

* Results of studies pertaining to homologous and heterologous immunity following apparent or possible inapparent infections with viruses SH and I.H. Pa. Expected average incidence of hepatitis in normal persons (no previous inoculations or history of hepatitis) of this age group inoculated with these viruses for the first time were as follows: Virus SH parenteral, 72 per cent; Virus I.H. Pa. oral, 74 per cent, parenteral, 11 per cent; Virus I.H. S. oral, 50 per cent on basis of small control group.

Table 2 indicates some of the differences between these diseases which are now known. Table 3 indicates the results of an experiment described elsewhere [12] on cross-immunity between two strains of infectious (epidemic) hepatitis virus and a strain of serum hepatitis virus, which suggest that the two viruses differ in their antigenic properties. One point appears to be of particular importance, namely, that in infectious (epidemic) hepatitis the incidence rapidly decreases after the age of 30 years, whereas the evidence thus far available does not indicate a similar tendency in serum hepatitis. As previously mentioned, a general immunization of the population during the early years apparently occurs in infectious (epidemic) hepatitis, whereas this may not occur in serum hepatitis. If this occurred in serum hepatitis it would be more difficult to explain the hepatitis resulting from the use of the plasma pools in battle casualties.

The presence of antibodies cannot readily be determined by serological means, as in mumps, and thus one can only infer from epidemiologic evidence and from the protective effect of the gamma globulin (see below) that a major portion of the general population is immunized during the early years of life from apparent or inapparent infection with the virus of infectious (epidemic) hepatitis. The experience during the recent war period with different epidemics of infectious (epidemic) hepatitis suggests that clinical cases without jaundice may be nearly as frequent as those with jaundice.

TABLE IV

Cases of Hepatitis with Jaundice Following Date of Injection with Globulin

Group	Total Injected	Jaundice Cases	Incidence, Per Cent	Total Controls	Jaundice Cases	Incidence, Per Cent
1	406	4	1	683	25	3.7
2	831	3	0.4	8,270	283	3.4
3	495	2	0.4	1,373	27	2.0

Table 4 illustrates the protection afforded against infectious (epidemic) hepatitis by a dose of 10 ml. of gamma globulin in certain units of the 5th Army during the fall and winter of 1944 to 1945. The final results, as gathered later by workers in the field, have demonstrated even more strikingly the value of gamma globulin for passive immunization in this disease. In addition to three epidemics studied with Captain S. S. Gellis [13] and Captain J. R. Neefe,[14] two in the Mediterranean Theatre of Operations and one in the United States, Dr. J. R. Paul of New Haven [15] and Major W. P. Havens, Jr., have reported a similarly favorable result. The protection afforded appears to be effective for a period of from six to eight weeks, inasmuch as the long incubation period offers a more adequate opportunity for passive protection than in such a disease as measles. The protective dosage has been demonstrated to be as small as approximately .06 ml. per pound of body weight, and may prove to be even smaller.

In contrast to the value of gamma globulin in prevention of infectious (epidemic) hepatitis, no value in treatment of the active disease could be demonstrated in limited studies conducted with Captain S. S. Gellis in the Mediterranean Theatre [13] during the autumn and winter of 1944 to 1945. These studies were not sufficient to be conclusive and it was possible to treat only a few cases within the first few days of onset. Treatment of infectious (epidemic) hepatitis with gamma globulin deserves further trial.

The value of gamma globulin in the prevention of serum hepatitis remains an interesting problem. Studies were initiated in two large general hospitals in this country among battle casualties who had received blood or plasma or both at the time of injury in various theatres of war. In one hospital [16] in which alternate casualties were injected with gamma globulin —10 ml. in a single dose—the incidence of hepatitis in the injected group did not differ significantly from the incidence of the disease in the controls. However, the average incubation period in the injected group was significantly longer than the average incubation period in the controls. The chance of this average delay in the incubation period not being due to the injection of the globulin was calculated as approximately one in four hundred. In another general hospital [17] which suffered a considerably higher incidence of serum hepatitis, alternate casualties were injected with two doses of 10 ml. each of gamma globulin at an interval of 30 days. The use of two doses appeared to be considerably more successful than a single dose in that the ratio of cases of hepatitis in the control group to cases in the

injected group was as seven to one. The chance distribution of the alternate cases in this hospital was indicated by the fact that the various percentages of casualties from the three different theatres of war—European, Mediterranean, and Pacific—were almost identical in the injected and control groups. The only additional general hospital from which data have been obtained as to the results of a single injection of gamma globulin, 10 ml. in all transfused battle casualties reported that the average incubation period of all cases of serum hepatitis was considerably increased over the average incubation period in those cases which occurred before the use of gamma globulin was started. Such data are difficult to evaluate until there is an opportunity of studying further the effect of multiple or larger doses of the globulin in controlling the disease.

In view of the fact that the incidence of infectious (epidemic) hepatitis falls off rapidly after approximately 30 years of age and that no such change has been demonstrated in serum hepatitis, it is difficult to believe that gamma globulin from large pools of adult plasma would be as highly effective in serum hepatitis as in epidemic or infectious hepatitis.

Poliomyelitis. When gamma globulin from the American Red Cross pools became available, Dr. Sydney Kramer at Michigan, and Dr. Werner Henle and I in Philadelphia were all equally interested in determining the presence of neutralizing antibodies against the Lansing strain of poliomyelitis virus. Neutralization tests were conducted in both laboratories when the material first became available and the presence of large amounts of such antibodies was demonstrated. It also became apparent that a very small amount of gamma globulin, 0.1 ml. injected intraperitoneally, would usually protect a mouse, even when the virus was injected intracerebrally at the same time. Further studies conducted by Kramer in cotton rats and monkeys have confirmed its protective value in these animals similar to that originally demonstrated in mice.

The interest in these findings lies not so much in their practical application, which appears highly problematical in view of the low incidence of the disease in man, but rather in the fact that despite the low incidence of the clinical disease, the relatively large amounts of antibodies present would suggest an immunization of the general population, which could perhaps best be explained by subclinical or inapparent infections. This also confirms earlier antibody studies by Kramer [18] and Aycock.[19] There are obviously other possible explanations which in view of the present findings appear less plausible.

Due to the expensive and time-consuming neutralization test in mice, cotton rats, or monkeys, and the variation in virus strains one can only infer, as in infectious hepatitis, on epidemiologic evidence and from the protective effect of the gamma globulin that immunization of a major portion of the general population occurs during the early years of life from mild clinical or subclinical (inapparent) infections. In poliomyelitis this point remains of major importance for investigation, namely, to determine

at what age in different geographical areas antibodies appear in groups of children studied longitudinally and both individually and collectively.

In animals, treatment with gamma globulin has proved totally ineffective and injection of large amounts of gamma globulin during the incubation period even well in advance of the earliest onset of the disease has not appeared to decrease its severity when the virus is injected intracerebrally.

During a recent severe epidemic of poliomyelitis Perkins and Bahlke [20] of the New York State Department of Health demonstrated that large doses of gamma globulin injected parenterally as treatment in alternate preparalytic cases had no effect on the course or outcome of the disease. The use of large amounts of gamma globulin for the study of passive protection of animals infected by more natural routes deserves continued investigation.

Rubella. Due particularly to the serious consequences to the fetus often attendant upon rubella in the mother during early pregnancy, as first reported from Australia by N. M. Gregg [21] and confirmed by many other workers, passive protection against this disease in the pregnant woman assumes an added significance. In 1943 and 1944 two experiments on rubella were conducted in Philadelphia, one at the University of Pennsylvania Hospital and one with Dr. Waldo Nelson at Temple University Hospital. In the first study, a nurse with rubella intimately exposed five room-mates who had no history of the disease. No secondary cases developed following the injection of 5 ml. of gamma globulin four days after exposure in each of the presumably susceptible adults. In the second study, an infant with rubella intimately exposed to the disease a ward of 13 infants and children who were presumably susceptible. No secondary cases developed following the injection of 2 ml. of gamma globulin four days after exposure. These results are recorded only for the purpose of suggesting the need for additional studies in this field. As in the other diseases mentioned, the major portion of the population appears to be immunized in early life.

Conclusions

1. Many epidemic diseases of childhood gradually immunize the general population both by apparent and inapparent cases and leave in passage considerable amounts of antibodies in adult plasma.

2. When such adult plasma is pooled from thousands of individuals it probably contains fairly uniform titers of antibodies, the changes in which, if readily measurable, afford an index of epidemic trends.

3. Gamma globulin from fractionated pools of plasma concentrates and preserves such antibodies in a readily usable form, which thus far apparently has been free from the danger of serum hepatitis.

4. The amount of specific protective antibodies in the gamma globulin and their effectiveness against each epidemic disease obviously differs and must be determined in each disease. In certain epidemic diseases outlined, they are highly effective.

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HEMOPHILIA: THE CLINICAL USE OF ANTI-HEMOPHILIC GLOBULIN *

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THE beneficial effect of whole blood transfusion in hemophilia has been recognized for over 30 years. The marked fall in the coagulation time following the transfusion of normal blood was attributed in 1916 by Minot and Lee[1] to the platelets. Patek and Stetson reinvestigated the problem in 1936. They confirmed the findings of Minot and Lee but showed that plasma free of formed elements including blood platelets had an effect similar to that of whole blood. Patek and Stetson proposed the thesis that the beneficial effect of whole blood transfusion in hemophilia was due to a factor or factors residing in the blood plasma. The prolonged coagulation time in hemophilia was due in the opinion of these authors to a deficiency of the plasma factors.[2]

In a series of reports from the Thorndike Memorial Laboratory over the past 12 years it has been shown that the antihemophilic property of platelet free plasma was closely associated with the globulin fraction of the plasma proteins. It has also been shown that the antihemophilic factor is neither prothrombin nor fibrinogen. Globulin fractions of normal human plasma were prepared free from both prothrombin and fibrinogen which had optimal effect in reducing the prolonged coagulation time of hemophilic patients to normal both in vitro and in vivo.

As E. J. Cohn has intimated, during the war large quantities of the plasma globulins obtained as a by-product from the preparation of human albumin, became available for physiologic study. In vitro studies of Cohn's fractions [3] showed that Fractions I, II and III had marked antihemophilic activity. Fraction IV had on occasion slight activity while Fraction V, the albumin fraction itself, had none.

Since it was known that Fraction I, that is, the fraction containing from 60 to 90 per cent of fibrinogen, could be injected into humans, in vivo studies were commenced on this fraction.[4] There is no implication that Fraction I is the best source of antihemophilic potency but its availability in sterile dried form offered a convenient starting point for investigation. As shown in figure 1 as little as 11 mg. of Fraction I injected intravenously into a case of hemophilia caused a marked drop in the coagulation time, whereas amounts of between 200 and 400 mg. gave optimal effects. The injection of preparations of Fraction I were comparable in their antihemophilic effect with those obtained following the injection of whole blood or plasma (figure 2).

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The effect of intramuscular injections of Fraction I seems to be unpredictable when administered to adult patients even when massage and heat are used at the site of injection.

Fraction I contains the fibrinogen of blood plasma as well as small amounts of prothrombin. Since our earlier work [5, 6, 7, 8] indicated that neither of these proteins was responsible for the antihemophilic properties of plasma, it was important to remove these substances from Fraction I. This step was accomplished by heating a solution of Fraction I to 56° C. for five minutes and filtering. The filtrate contained no fibrinogen and only traces of prothrombin. However, it was as active as a source of antihemophilic activity as the whole fraction from which it was prepared. This

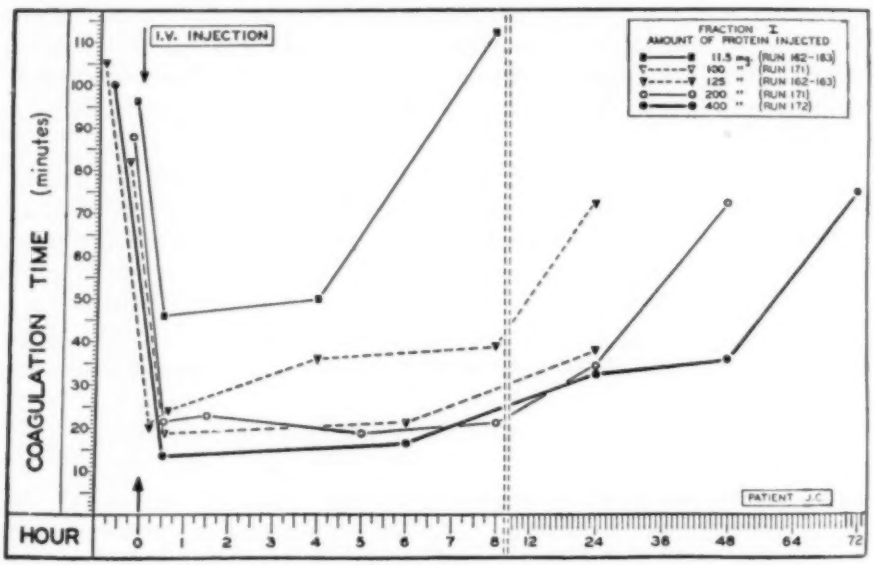

FIG. 1.

observation makes it probable that the antihemophilic property of plasma may be concentrated in a few milligrams of material, offering possibly an opportunity for a therapeutic approach to hemophilia.

At the present time two important matters must be clearly understood. The preparations of Fraction I vary a great deal in their antihemophilic potency. This can only be remedied after further study of the preparations in order to obtain satisfactory criteria. Secondly, as increased purity is obtained some cases of hemophilia fail to respond to the injection of Fraction I although they respond to crude preparations of plasma proteins and to plasma. It has been assumed for some years that the deficiency in hemophilia is not necessarily a single factor. Therefore, in patients who fail to respond to Fraction I, other of the globulin fractions must be investigated as soon as suitable preparations for intravenous human use are obtained.

The injection of Fraction I may be used in the preparation of patients with hemophilia for dental extraction. The use of Fraction I for the control of hemorrhage in hemophilia is under investigation. A much more extensive clinical trial is necessary to evaluate the usefulness of the preparation for this purpose. The results so far have been promising. No refractory phase has been obtained following the injection of Fraction I and no untoward reactions following the injection of the material have been observed. The dose of the material required to control hemorrhage varies from patient to patient. At present 400 mg. of the material in 20 c.c. of isotonic salt solution is used as an initial dose. In preparing patients for operative procedures multiple injections may be employed on the day pre-

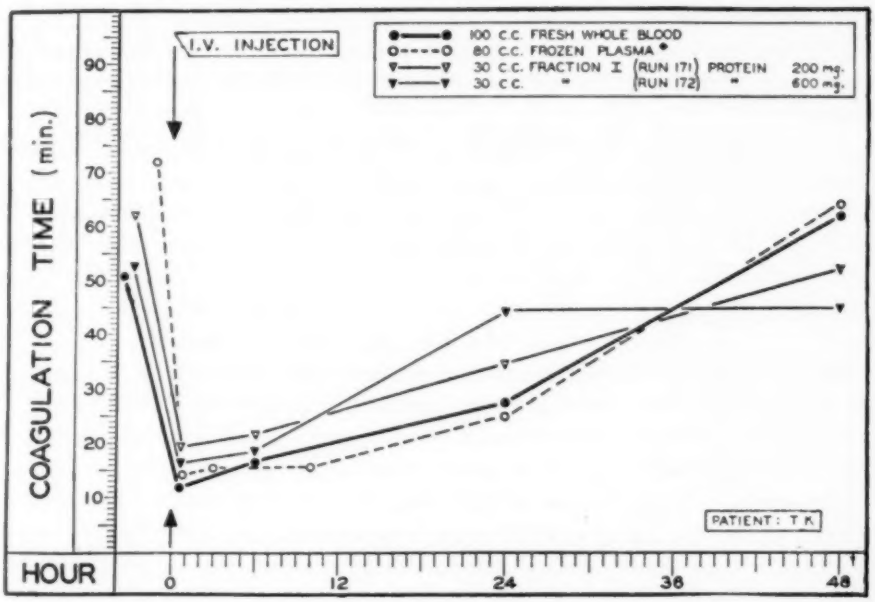

FIG. 2.

ceding the operation. However, if the patient is already anemic due to repeated hemorrhage, it is essential that whole blood be used rather than only plasma or antihemophilic globulin.

Of equal importance to the control of the blood coagulation time, in hemophilia, is the control of local hemorrhage when it occurs. The availability of a good hemostatic agent for this purpose is desirable. Antihemophilic globulin has some hemostatic properties. However, since this material produces clotting of blood by activating the blood coagulation reaction, its effects require a matter of minutes to develop. On the other hand, thrombin preparations which act directly on fibrinogen to produce fibrin clots require only seconds to produce this effect. For this reason, thrombin is an ideal hemostatic agent.

As Dr. Cohn has pointed out, preparations rich in prothrombin can be obtained by suitable fractionation of the plasma globulins. Prothrombin can be converted to thrombin by interaction with tissue thromboplastin derived from brain, lung, placenta or other tissues. The thrombin so obtained may be spread on or impregnated into sterile gauze, fibrin foams or absorbable cellulose and applied with pressure to the bleeding point. It is important that the highest possible concentration of thrombin be applied to the lesion. For this reason we favor the direct application of packs containing powdered thrombin rather than liquid preparations which may wash away rather quickly from the wound. Preparations of human thrombin and absorbable non-reactive sponges are of importance for use in wounds which later are to be closed by suture. For open local hemostasis thrombin from animal sources may be employed.

The application of animal thrombin to local wounds has been employed for some years in our clinic with no indication of local or systemic sensitivity reaction.

A thrombin preparation has been made by Parfentjev from rabbit plasma by simple salting out procedures requiring no activation with thromboplastin. We have made similar preparations from the plasma of swine, steers and humans.[9] This preparation is available under the commercial name of "Hemostatic Globulin" and is an extremely potent hemostatic agent. Thrombin preparations *must never* be injected parenterally due to the fact that they can produce intravascular clotting and profound shock.[10]

The availability of thrombin preparations has reduced enormously the risk of surgical procedures among hemophilic patients. Prior to the development of powerful hemostatics, simple procedures such as dental extractions in hemophilic patients were attended by at least the risk of profound anemia. Since the use of thrombin in our hemophilic clinic over the past ten years, bleeding has been well controlled following operative procedures, such as dental extractions, amputation and skin grafting and no serious sequelae have developed.

Further progress may be noted in the development of therapeutic agents for the treatment of hemophilic hemorrhage. Material for this purpose which may be contained in a small enough volume to permit its prophylactic use by hemophilic patients is an ultimate aim. Such material may be used to advantage in the preparation of hemophilic patients for operation. So far our experience along these lines has been with the use of our own globulin preparations and Fraction I of Cohn. Standardization of the commercial methods of preparation of this substance is required and a careful assay of the in vivo activity of other fractions is necessary.

In addition to decreasing the coagulation time of hemophilic blood by the use of globulin preparations, progress has been made in the development and utilization of thrombin preparations for the control of hemorrhage. The introduction of such hemostatics has markedly lowered the dangers attendant upon surgical operations on hemophilic patients.

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OTHER USES OF PLASMA FRACTIONS WITH PARTICULAR REFERENCE TO SERUM ALBUMIN *

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INTRODUCTION

Most clinical studies with plasma fractions thus far have been based on knowledge concerning the physiology of the plasma proteins which was already available, so that investigation has consisted of the verification of predictions which could be made on a priori grounds. In the future, however, the studies should enter a more exciting phase when we shall be exploring unknown territory. Cohn [1] has discussed a rather new conception of the function of the plasma proteins, namely, their importance as vehicles for the transport of substances of low molecular weight or of water-insoluble lipoids. He has also indicated that it is possible to separate certain fractions from the plasma globulins, in which hormonal or enzymatic activity, such as that of serum esterase, is very highly concentrated in comparison with pooled normal plasma. The clinical and physiological importance of such proteins as the serum globulin with esterase activity, the β-globulin with capacity to bind free iron, and the lipoproteins of plasma, is a field for investigation which opens up many inviting prospects. At present we are only in the initial stages, when the all-important work of determining the safety of these preparations for clinical use is just beginning.

USES OF THE GLOBULIN FRACTIONS

Stokes [2] has indicated the progress which has been made in the application of a highly purified gamma globulin fraction, containing most of the antibody activity of pooled plasma, to the control of infectious diseases. Minot and Taylor [3] have summarized the present status of investigations with a fibrinogen fraction, in which there is found that component of the normal clotting mechanism which appears to be deficient in the plasma of most patients with hemophilia. Before proceeding to a discussion of serum albumin, certain other products of the fractionation of human plasma deserve a brief word. Although Fraction I is of interest to medical men because of its anti-hemophiliac activity, it is of far greater interest to surgeons because of its content of fibrinogen. In combination with human thrombin, derived from Fraction III, it has been used to promote adherence of skin

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grafts,[4] and to form a coagulum around calculi in the renal pelvis so as to effect their complete removal without fragmentation.[5] In the form of fibrin foam with thrombin the clotting proteins have been widely and successfully used to accomplish rapid hemostasis in neurosurgical[6] and certain other surgical procedures.[7] Fibrin film has provided the surgeon with a pliable, transparent, and relatively tough membrane which does not excite a significant tissue reaction but which is gradually replaced with connective tissue without the formation of adhesions to underlying structures. These properties have made it very valuable to the neurosurgeon as an aid in the repair of operative or traumatic defects of the dura mater.[8] The anti-A and anti-B isoagglutinins and anti-Rh globulin derived from Fraction III–1 by concentration of this activity from pooled group-specific or anti-Rh plasma[9, 10, 11] provide potent, dependable reagents for grouping blood which should increase the safety of transfusions of either whole blood or of resuspended red cells.

Uses of the Albumin Fraction

Plasma fractions have contributed to medical progress in two ways: first, as new therapeutic agents, with which it is possible frequently to attain certain objectives which cannot be readily attained with the plasma from which they are derived; and second, as new tools for the study of physiological and pathological processes. The various studies on serum albumin, although by no means complete, illustrate this dual rôle of plasma fractions very clearly.

Albumin as a Therapeutic Agent

Normal human serum albumin was primarily developed, in response to an urgent request from the Armed Forces, as a blood substitute for use in traumatic shock. Because its chemical properties make possible its distribution in a stable, concentrated solution, it is compact to transport and convenient to use.[12] Moreover, the stability of salt-poor albumin in its new diluent, containing but 0.3 gram per cent of sodium and .04 M acetyl-d-l-tryptophane for stabilization, is so great that it can be heated for 10 hours at 60° C. in the final container before distribution.[13] This has made it possible to eliminate any preservative with potential injurious effects, such as the mercurials and should, we believe, obviate the possibility of transmission of viruses, such as the agent of homologous serum jaundice. Clinical experience has also shown that with the elimination of practically all of the globulins, albumin solutions rarely give rise to any immediate reactions, other than occasional pyrogenic reactions or those dependent on their physiological property of increasing plasma volume.[14] In this connection it is worth emphasizing that concentrated albumin, unlike concentrated plasma or gelatin, is only as viscous as whole blood with a hematocrit reading of 50 per cent,[15] and when injected lowers blood viscosity owing to hemodilution. This probably accounts for the fact that it appears to be

more readily tolerated by patients with mild congestive failure than whole blood or other more viscous colloidal solutions.

In the treatment of shock, albumin appears to be an effective blood substitute. Stead and Ebert [16] demonstrated that, if blood was removed rapidly by venesection from human subjects and concentrated albumin administered, there was a much greater increase in plasma volume than could be accounted for by the solution injected, indicating transfer of fluid into the circulation due to the osmotic effect of the albumin. In studies on a larger group of subjects, it was shown that the increase in plasma volume in such experiments approximated closely that expected on the basis of osmotic pressure measurements in vitro.[17] In several clinical studies on the use of albumin in shock [18, 19, 20] the expected results were obtained, namely increased plasma volume as shown by hemodilution or by dye measurements and clinical improvement. Studies of circulatory dynamics in shock patients receiving albumin showed that improvement after albumin therapy was associated with an increase in cardiac output,[19, 20] which was greater than that produced by the administration of whole blood.[20] This greater increase in output was interpreted as evidence of the fact that when traumatic shock, due primarily to loss of blood, was treated with albumin (or plasma) the deficit in blood volume was made good, but the patient was left with an anemia, necessitating a more rapid circulation of the remaining hemoglobin to provide oxygen for the tissues.

Fears concerning the use of albumin in the treatment of shock have arisen in the minds of many physicians primarily because they have failed to appreciate that, although it is distributed in 25 per cent solution for convenience, it does not have to be used in that form. There is abundant experimental and clinical evidence that when concentrated albumin is administered to patients with diminished blood volume due to hemorrhage, trauma, or burns, it usually produces both clinical improvement and a considerably greater increase in plasma volume than can be accounted for by the volume of solution injected. However, the administration of additional saline enhances the effect of albumin (table 1). In severely dehydrated patients in shock, already depleted of water or of water and electrolytes, it is obvious that the administration of colloid alone will not suffice to restore the circulation. It should be emphasized that there is no evidence that concentrated albumin is harmful even in severe dehydration, presumably because of its comparatively low viscosity. The experimental work of Fine and his colleagues [21] has confirmed these conclusions and has demonstrated that in dogs additional fluids may be administered to supplement concentrated albumin by way of the gastrointestinal tract or by vein with the albumin. A 5 per cent albumin solution in 0.85 per cent saline solution is approximately isosmotic and isotonic with citrated human plasma. Therefore each 100 c.c. of 25 per cent albumin solution should be supplemented with 400 to 500 c.c. of saline solution, when possible, in the treatment of shock.

TABLE I

Osmotic Effect of Concentrated Albumin
From Plasma Volume Measurements Made within 1½ Hours of Injection of Albumin

Type of Case	No. Cases	Plasma Volume Increase c.c./gram of injected albumin	
		Spread	Average
Calculated from osmotic pressure measurements[1]			18
Experimental hemorrhage in man[2]	11	13.2–24.1	17.4
Clinical shock[3] (*no additional saline or small amount*)	63	0–31.7	11.7
Clinical shock[3] (*additional saline*)	20	7–29	17.9

[1] SCATCHARD, G., BATCHELDER, A. C., and BROWN, A.: The osmotic pressure of plasma and serum albumin, Jr. Clin. Invest., 1944, xxiii, 458–465.
[2] HEYL, J. T., GIBSON, J. G., II, and JANEWAY, C. A.[17]
[3] From published data of COURNAND, A., NOBLE, R. P., BREED, E. S., LAWSON, H. D., BALDWIN, E. DeF., PINCHOT, G. B., and RICHARDS, D. W., JR.[20] and WARREN, J. V., STEAD, E. A., JR., MERRILL, A. J., and BRANNON, E. S.,[19] and unpublished data from a study of albumin carried on under direction of Dr. Dickinson Richards for the Committee on Medical Research. Data collected by Cournand and Lowell, Stead and Warren, and Evans.

Experience during the war has demonstrated that traumatic shock, in military or civilian practice, is primarily due to loss of whole blood, unless plasma loss due to burns or peritoneal irritation occurs. Hence optimal treatment requires the use of whole blood to avoid the anemia which develops if plasma or albumin is administered for replacement.[20] The latter two agents may be very useful for emergency supportive therapy, and, despite a recent report in which concentrated albumin was compared unfavorably with isotonic plasma,[22] there is no reason why albumin with saline, either by vein or by mouth, if it can be taken, should not be quite as satisfactory as the latter.

While albumin should be supplemented with fluids in the treatment of shock, in hypoproteinemic edema concentrated low-salt albumin provides exactly that combination of properties needed for rational therapy.* Certain general statements concerning the use of albumin in hypoproteinemia may be made on the basis of present experience. First, the patient should be on a high caloric diet, with an adequate protein intake, if possible, in order to avoid utilization of the injected albumin as a source of energy. Second, doses of 50 grams daily should be used in adults unless there is congestive failure. This may be given in two doses or mixed with 200 to 300 c.c. of

* Clinical experience with the use of albumin in the many conditions encountered in civilian medicine where its value might be anticipated has of necessity been quite limited by the fact that albumin was developed and produced for the Armed Forces as a blood substitute during the war. At present albumin can only be obtained from one commercial laboratory, although it may be available before long in two states as a result of their blood programs. The statements about albumin in hypoproteinemia are based on a very limited experience with a fairly small number of patients, and further careful clinical investigation is urgently needed to define the place of albumin in therapy more exactly.

10 per cent glucose and infused by intravenous drip over a period of several hours. Third, a considerably larger amount must be given than would be expected on the basis of the deficit in circulating albumin. Fourth, injected albumin will not ordinarily appear in the urine unless there is proteinuria already.

Hypoproteinemia is rarely the result of a single factor, but usually of a combination of inadequate food intake, protein loss, and increased catabolism incident to serious illness, injury, or surgical procedure. Abundant food is obviously the best treatment for hypoproteinemia, while intravenous alimentation with a solution of amino acids or hydrolyzed protein is rational as a supplement to or substitute for oral feeding when necessary. However, there are times when it is important to relieve edema promptly in order to promote healing or to relieve symptoms, such as obstruction at an intestinal anastomosis, pulmonary congestion, or circulatory inadequacy with oliguria when these are the result of hypoproteinemia. Before the introduction of albumin, the clinician was well provided with solutions—glucose, saline, and sodium lactate or bicarbonate for repair of dehydration and acidosis but he was not well equipped to deal with edema. Plasma has certain drawbacks—first, the large amount of water and sodium salts which must be given with the protein, second, the fact that only half its protein is albumin, which has the greatest osmotic activity, and third, the chance that it may give rise to homologous serum jaundice in an occasional recipient. In a few patients with acute but reversible hypoproteinemia, the administration of albumin in large doses has elevated the level of serum albumin rapidly with diuresis, even during periods of increased catabolism when intravenous amino acids produced little benefit.[23, 24] This should make albumin very useful to internists, surgeons, pediatricians, and obstetricians, all of whom frequently see patients who need prompt relief for hypoproteinemic edema. In addition to the relief of generalized edema, albumin deserves further study as a means of controlling local edema in such sites as the brain, lungs, and gastrointestinal tract where it gives rise to symptoms. Little is known of its usefulness under these circumstances.

Hypoalbuminemia is a frequent accompaniment of diffuse disease of the liver. In cirrhosis, intravenous albumin, in doses of 25 to 50 grams daily in addition to an adequate diet, will raise the serum albumin level to normal in one to two weeks. This change in serum proteins is associated with an increase in sense of well-being, disappearance of peripheral edema, and usually some diminution of ascites.[14, 25, 26] In advanced cases there is apt to be a fall in serum albumin with a gradual return of symptoms when treatment is discontinued. In patients with hepatitis, the lesions in the liver are reversible, and albumin therapy has been used with great benefit when it was indicated by the occurrence of hypoalbuminemia.[27, 28]

Of all types of edema none is so stubborn nor so unpredictable as that associated with the chronic stages of renal disease. Patients may remain bedridden for months on end and then suddenly, for no apparent reason,

begin to exhibit a profuse diuresis. There is little doubt of the importance of reduced colloid osmotic pressure in the production of this form of edema, and hence albumin would appear to be the obvious physiological diuretic agent. That concentrated albumin, and particularly salt-poor albumin, will produce a diuresis in many patients with the nephrotic syndrome, much as acacia does but without its harmful after-effects [25, 29] seems clear from the accumulated experience so far. However, it is equally clear that diuresis does *not* follow albumin administration in certain patients, that it usually lasts only as long as albumin is administered,[30] and that massive doses of albumin (50 grams daily for 20 to 30 days in an adult) are needed to rid the patient of edema and to produce any significant rise of the plasma protein level.[25] A large part of the albumin injected appears in the urine during the 48 hours after a single injection.[29, 31] Thus, the use of albumin in nephrosis is exceedingly wasteful, but deserves further study in cases which are resistant to simple methods of treatment. It should be added that there are those who believe that the massive proteinuria which occurs with albumin therapy may in itself produce kidney damage.

In acute renal failure albumin may be very useful.[32] If oliguria is the result of the poor renal circulation arising from hypoproteinemia and not of primary kidney damage, it may mobilize water and allow the kidney to function. If oliguria or anuria is the result of primary renal damage, as in acute nephritis or sulfadiazine intoxication, albumin may be used to maintain an adequate serum protein level without elevation of the non-protein nitrogen, provided sufficient calories are administered to spare protein catabolism. This is in line with the present feeling that the best treatment for anuria is to keep the chemical composition of the body fluids as normal as possible by parenteral and oral administration of carbohydrate, fluid, and electrolytes under rigid laboratory control.[33] Thus the patient is kept alive until spontaneous repair of the renal lesion leads to a return of the excretory function.

Albumin as an Experimental Tool

For short-term physiological studies in animals, bovine albumin, crystallized by the method of Cohn and Hughes [34] is an ideal experimental colloid. Its physical properties are well known and standardized, and, being almost completely free of globulins, its injection does not produce the immediate reactions seen when bovine plasma is given to dogs. It has been used in a series of fundamental studies on the hemodynamics of shock. Fine and his colleagues have used it to investigate the relative importance of colloid and saline in the therapy of tourniquet shock [21] and also the importance of blood viscosity in the irreversibility of shock.[35, 36] Other workers have used crystallized bovine albumin in investigations on various aspects of experimental burn shock.[37] Chemists have found in bovine albumin a pure protein conveniently available for investigations on such problems as the interaction of proteins with other substances and the despeciation and denaturation of proteins.[38] It has been used to provide a

medium of controlled density for studies on the size of virus particles in work which has important practical bearing on the preparation of virus vaccines.[39]

The introduction of human albumin into medicine has provided the clinician with a tool for attacking certain aspects of the pathogenesis of edema which have been in dispute for many years. Previously our knowledge of the function of albumin has been gained principally from the observation of those slow, spontaneous changes which occur in the natural course of disease. Thus, clinical observations on patients with cirrhosis of the liver have indicated that lowering of the serum albumin was an important factor in the production of ascites.[40] Such observations are similar to those made by endocrinologists when ablation of a particular gland was the only available method for experimental study of its function. With the development of potent hormone preparations, the problem could be defined much more clearly by trials of substitution therapy. When albumin has been given to a few patients with cirrhosis until normal levels of serum albumin have been achieved peripheral edema has disappeared very rapidly, while ascites has diminished much more slowly. This indicates that other factors than a lowered colloid osmotic pressure of the blood are important in the production of ascites, among them back pressure in the portal vein, changes in the absorptive power of the peritoneal surfaces, and antidiuretic substances.

In the case of nephrosis, the use of albumin has helped to clarify but not to solve the problem of edema formation. The fact that "spontaneous diuresis" following infection may produce a far greater outpouring of urine than the administration of enough albumin to produce a more striking though temporary increase in serum albumin suggests that water balance is under the control of factors other than the serum albumin level in this disease. During albumin therapy, nephrotic patients excrete greatly increased amounts of protein in their urine. By fractionation of a large amount of urine collected from a nephrotic patient during a period of treatment,[29] an albumin fraction was obtained which appeared to resemble normal human serum albumin in its physical and immunological properties, although it was very toxic when injected into animals. This suggests that the nephrotic cannot retain normal serum albumin and is evidence for the concept that proteinuria is due to a renal lesion rather than to a defect of the plasma proteins. Much more extensive work along such lines as these will have to be done, but these examples serve to illustrate the way in which purified plasma proteins may be used to develop understanding of the pathogenesis of important physiological disturbances in disease.

Summary

The use of serum albumin in treatment and investigation has been reviewed. There are gaps to be filled in, but enough has already been done to show how concentrated human albumin provides the clinician with an important therapeutic agent for emergency use in shock and for the treatment

of hypoproteinemic edema, and the investigator with a valuable tool for the study of those conditions in which the concentration of this component in plasma is disturbed.

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BRONCHIOGENIC CARCINOMA; AN ANALYSIS OF 343 CASES *

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Prior to 1933 when Graham reported the first successful pneumonectomy for bronchiogenic carcinoma, the disease was considered rare. Diagnostic methods were inadequate, there was no curative treatment and interest in the subject was entirely academic. Hundreds of successful pneumonectomies have now been performed by many surgeons. But a careful study of large groups of cases reveals an appalling and unnecessarily low incidence of operability. There are, unfortunately, two periods of delay during which periods the patient may forfeit his chance for cure. The first is between the onset of symptoms and medical consultation and the second is that between the *first medical consultation and a positive diagnosis.* Further improvement in results can come only with a reduction in the total time between the onset of symptoms and the institution of treatment. Careful analysis of large groups of cases must be made in an effort to bring out data which will be helpful in eliminating or reducing to a minimum these periods of delay. Several such reports have appeared recently.[1, 2, 3] With this in mind, a careful survey was made of 343 cases of pulmonary carcinoma from various services at the University of Michigan Hospital. This communication is a report of the results of that study. The cases cover the six year period from January 1, 1938 to January 1, 1944.

For purposes of study, the cases have been divided into two groups. Group 1 comprises 112 cases in which histologic confirmation was lacking although clinically and roentgenologically the diagnosis of bronchial cancer was justified. Several factors entered into the inability to secure adequate confirmation of the diagnosis; the disease had progressed too far to warrant further study, the patient refused further examination or there was a peripheral type of lesion which was inaccessible to bronchoscopic vision. No detailed study was made of this group. Group 2 consists of 231 cases, histologically confirmed, and is further divided into two sub-groups: (1) those who were considered inoperable at the time of the diagnosis or those who refused surgery, and (2) those who had operation, either resection or exploratory thoracotomy. Group 2 cases are considered in detail.

Incidence

That the increased incidence of bronchiogenic carcinoma is both relative and absolute is an accepted fact. Many articles in support of this have appeared in the past few years and the reader is referred to the recent article by

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Ochsner, Dixon and DeBakey[1] for a splendid inclusive review of the literature and complete bibliography on the subject.

During the six year period covered by this study there were 177,005 registrations at the University Hospital. This includes both in-patients and out-patients. The incidence of bronchiogenic carcinoma in this group is given in table 1 where it may be compared with the incidence during the preceding five year period, 1933–1938.[4]

TABLE I

Incidence of Bronchiogenic Carcinoma
University of Michigan Hospital

	Registrations	Bronchiogenic Carcinoma	Cases Proved Histologically	Incidence Per 10,000 Cases	Increase Per 10,000 Cases
1933–1938	152,150	137	100	8.99	
1938–1944	177,005	343	231	13.00	4.01

Sex. It is a widely accepted fact that bronchiogenic carcinoma is predominantly a disease of the male sex. Various collected series of cases show the occurrence in men to be from 70 to 90 per cent of all cases.[1, 2] In the 100 proved cases in the early University Hospital series, 82 per cent were males. In the present series, 83.6 per cent of the inoperable cases and 90.0 per cent of the operable group were men.

Age. Carcinoma, whether of the lung or elsewhere, is essentially a disease of advancing years with the majority of cases occurring between 40 and 60 years of age. In the group under discussion, the youngest patient was 18 years of age and the oldest was 77. Age, per se, appears to have no effect on operability. Table 2 gives the age incidence by decades.

TABLE II

Age Incidence
(231 Proved Cases)

Under 20		20 to 30		30 to 40		40 to 50		50 to 60		60 to 70		Over 70	
No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
2	.86	2	.86	14	6.1	64	28.8	97	41.9	47	20.3	5	2.2

ETIOLOGY

Much has been written about various factors which have been thought to play a part in the causation of pulmonary carcinoma.[1] The present study adds nothing to support any existing theories of etiology. However, the wide variety of recorded occupations does confirm the conclusion of others, that bronchiogenic carcinoma is not an occupational disease.

Pathology

Our conception of the pathology of pulmonary cancer has changed materially in the past 10 years. Prior to the development of resection, autopsy material was the chief source of study. Obviously most of these cases were late and unsuited for a study of the development and early manifestations of the disease.

The right lung is more frequently involved than the left. In the 343 cases included in this study, 203 or 59.2 per cent were located on the right side, 138 or 40.2 per cent on the left and in two cases or 0.6 per cent there was bilateral involvement. In a series of 4,732 cases collected from the literature by Ochsner,[1] 58.3 per cent of the tumors were in the right lung and 41.6 per cent were in the left lung.

Two main types of growth are recognized according to location in the lung, those which occur in the hilus and those which originate in the periphery of the lung. The majority occur close to the hilus. Pulmonary carcinoma spreads by direct extension and by lymphogenous and hematogenous metastasis. The most frequent sites of metastasis are, as is to be expected, the regional lymph nodes. In 100 per cent of the explored cases in which resection was not performed, these nodes were involved. Autopsy was performed on 41 of the 154 inoperable patients. Regional nodes were involved in every case. Next in frequency was spread, either by direct extension or metastasis, to one or both lungs. This occurred 19 times. The pleura and liver were involved 14 times each, the brain 10 times and one or more bones 9 times. These are late manifestations. Of greater practical importance are the types of spread which denoted inoperability in 154 cases at the time of diagnosis. The most frequent were: involvement of the pleura, 38 cases; supraclavicular nodes, 20 cases; recurrent laryngeal nerve paralysis, 18 cases; location of lesion at or above the main tracheal carina, 16 cases; cerebral metastasis, 11 cases; and bone metastasis, 9 cases. Phrenic nerve paralysis, direct extension to the chest wall, metastasis to the contralateral lung, to the axillary nodes, and to the liver and skin occurred with sufficient frequency to be noteworthy.

Bronchiogenic carcinoma at the University Hospital is classified into the squamous cell, the adenocarcinomatous (the gland cell type), and the undifferentiated types. The undifferentiated includes the small cell, the round cell and the oat cell types. All are graded, when possible, on a basis of 1 to 4. Although the University of Michigan Department of Pathology classifies the so-called bronchial adenomas as carcinoma, grade 1, these growths have been excluded from this study. This is in keeping with the policy of Graham [5] who states that his carcinoma statistics do not include adenomas unless they show definite evidence of spread. Two of the adenoma cases which had originally been classified as bronchiogenic carcinoma were thus excluded. Both had a pneumonectomy and both are living and well, one six and one five years after operation. In addition there is one case, operated on over 11 years ago, still living and well.

The squamous cell carcinoma is the most frequently found type (table 3) and it offers the best prognosis. The prognosis is poorest in the cases presenting the undifferentiated type. In the 43 cases suitable for resection, 29 or 67.4 per cent were squamous cell and of the 13 in this group still living, 8 or 61.5 per cent were of this variety.

TABLE III

Pathological Findings According to Cell Type

	Proved Cases		Inoperable Cases		Explored No Resection		Resected	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Squamous Cell	98	42.4	53	34.4	16	47.1	29	67.4
Adenocarcinoma	45	19.5	31	20.2	4	11.8	4	9.3
Undifferentiated	81	35.1	60	38.9	11	32.3	10	23.3
Not Classified	7	3.1	7	6.5	3	8.8		
Total	231	100.0	154	100.0	34	100.0	43	100.0

Adenocarcinoma was found more frequently in women. Of the 218 proved cases in which the growth was classified, there were 28 women and 190 men. Sixteen or 57.1 per cent of the female cases had adenocarcinoma whereas only 29 or 14.7 per cent were of this type in the male group. This preponderance of adenocarcinoma in women causes one to ponder on a possible relationship between it and the so-called bronchial adenoma. Both occur more frequently in women; both are pleomorphic, sections from different portions of the same tumor often revealing different appearances; and, finally, the glandular arrangement of the epithelium seen in some adenomas has caused some pathologists to diagnose them as adenocarcinoma.

In the follow-up of the series of patients operated on there have been 17 who have died following resection, and among these there were six known and one probable recurrence. Autopsy verification was available in five of these cases. In one case the resection was for palliative reasons only, all of the growth not being removed. In examining the cause of death of these 17 patients, empyema was found to account for four or 23.4 per cent. In two of these, the empyema developed late, six and nine months respectively after pneumonectomy. It is hoped that our present use of chemotherapy and penicillin will reduce this hazard to a negligible point.

Among the living patients of the operated series, all of whom have been followed to date, only one has shown evidence of a recurrence.

CLINICAL

Bronchiogenic carcinoma is often a relatively slowly growing tumor and the importance of early diagnosis and treatment has been stressed repeatedly. For this reason, a careful analysis was made of the time interval between the onset of the first symptoms and the diagnosis. In this connection it

must be emphasized that occasionally early symptoms are lacking or trivial and the first signs to present themselves are those of some serious metastatic lesion. Brain metastasis is a noteworthy example. Because of the frequent triviality of the initial symptoms, the patient does not seek immediate medical advice. An effort was made to determine the time between the onset of significant symptoms, and the first medical consultation. Unfortunately this information was lacking on the majority of histories, but it would appear that Overholt's [7] figures approximate those in this series, where this information was available. He found that in 125 cases the majority did not seek medical advice for three or more months after the onset of symptoms. For this delay the physician is not directly responsible. But he is most certainly responsible once he has been consulted. And here the figures are shocking. *In more than 50 per cent of the cases a diagnosis of bronchiogenic carcinoma was not made for six or more months after the patient sought medical advice.* Thus we find that in over half of the cases a positive diagnosis was not made until nine or more months after the onset of symptoms.

TABLE IV

Most Frequent Initial Symptoms

Symptom	Number	Per cent	
Cough	97	41.9	160 69.2%
Pneumonia "Flu" Cold	63	27.3	
Chest Pain	48	20.7	
Hemoptysis	30	12.9	
Dyspnea	21	9.0	
Ease of Fatigue	20	6.9	

A keen awareness of the initial symptoms is important. Table 4 lists the most frequent initial symptoms and the number of times they occurred. It must be remembered that the patient may have complained of any of them alone or of a combination of two or more. The chronic cigarette cough is so prevalent today that there is a tendency to ignore it. In the 97 instances in which cough is mentioned, however, it was an initial symptom. The incidence of cough is really greater than this 41.9 per cent would indicate. Those who first complained of a cold, "flu" or pneumonia also had a cough and if these two groups were combined the incidence of cough was 69.2 per cent. In patients who have a chronic cough, any change in its character is significant. Often a dry hacking cough, the cigarette type, becomes productive and even the slightest streaking with blood should call for careful study. The development of a wheeze is important. An attack of pneumonia, "flu" or a bad cold was given by 27.3 per cent of the patients as the beginning of their illness. The acute symptoms usually responded to treatment but the patient never felt well afterwards. Hemoptysis, which here denotes any amount of blood from a slight streaking to a frank hemorrhage, was present initially in 12.9 per cent of the cases. In several instances this symptom, together with loss of weight and a confusing roentgenogram of the

chest, led to prolonged hospitalization for pulmonary tuberculosis, in spite of a persistently negative sputum, and much valuable time was lost. Cancer was not suspected and bronchoscopy was not done. Pain was a first symptom in about one-third of the cases. Chest pain should be thoroughly investigated and not dismissed with a few strips of adhesive applied to the chest. Ease of fatigue and exertional dyspnea occurred with sufficient frequency to be considered important. Loss of weight is sometimes given as the first indication that something is wrong but it is usually a late manifestation. In 16 instances the disease was ushered in with symptoms not referable to the chest. Nausea and vomiting, abdominal pain, neurological symptoms and pain elsewhere in the body are mentioned. Arthritic pain in one or more joints had been noted, the pain clearing completely following resection of the pulmonary lesion. In one case clubbing of the fingers and toes was the first thing noted.

Diagnosis

The diagnosis of pulmonary carcinoma is usually not difficult. If successful surgical removal of the lesion is to be carried out, it is essential that the patient reach the surgeon at the earliest possible time after the onset of symptoms. If the physician will but bear in mind the possibility of the existence of the disease and carefully investigate all unexplained or prolonged respiratory complaints in all persons, particularly men, past 40 years of age, many lives will be saved.

Once that cancer has been suspected and the physical examination completed, a careful fluoroscopic and roentgen-ray study should be made. At the fluoroscope one notes the presence or absence of a lesion either close to the hilus or in the periphery of the lung. Widening of the mediastinum, retraction, indicating atelectasis, and free movement or fixation of the diaphragm should be looked for. Diaphragmatic motion is important as indicating whether or not the phrenic nerve is involved by mediastinal invasion. While it is obvious that a positive diagnosis cannot be made by roentgen-ray alone, the findings, as interpreted by an expert, give a high incidence of correct diagnosis. Occasionally one may encounter an early case in which the roentgenographic findings are negative. Many bizarre findings are often encountered and it is only by wide experience and a constant *suspicion* of the condition that a proper interpretation can be made. The shadow seen may be that of the tumor itself or secondary manifestations. Tuberculosis, bronchiectasis and lung abscess offer particularly difficult differential problems at times.

Bronchoscopy is by far the most important procedure in establishing a diagnosis. Biopsy can be taken and the location and extent of the growth in the bronchus or bronchial wall can be ascertained. Occasionally a lesion, grossly carcinomatous in appearance, is seen, even though the biopsy may be reported as negative. Repeated bronchoscopies will usually result in a positive histological diagnosis. Conversely, other lesions, such as tuber-

culomas, tuberculous bronchitis, tuberculous or pyogenic granulation tissue or benign tumor, may be present and seen at the time of the bronchoscopic examination. The exact location of the growth may be of great importance in deciding on the operability of the lesion. A lesion too close to, or involving the main carina, or one extending too far up along the lateral wall into the trachea, is obviously not removable. A positive bronchoscopic biopsy is, of course, dependent on the lesion's being located in one of the accessible bronchi or growing out of one of the primary or secondary branches. In the present series bronchoscopy was performed in all 77 of the operable cases and in 112 of the 154 inoperable group. Patients who were too ill or in whom there were obvious metastatic lesions, were not subjected to the procedure as the result would have been of academic interest only. Tissue for histological examination was obtained in 19 or 81.2 per cent of the inoperable group and in 47 or 61 per cent of those on whom operation was performed. However, the percentage of positive biopsies was nearly the same in the two groups, being 90.1 per cent and 86.3 per cent, respectively.

Bronchography is useful at times in that it may indicate an obstructed bronchus beyond the field of bronchoscopic vision. In certain cases this may be of definite value in the differential diagnosis.

Punch or aspiration biopsy was used four times in this series but it is a potentially dangerous procedure and is not recommended.

The presence of pleural fluid does not necessarily mean pleural metastasis but the finding of bloody pleural fluid is generally considered an indication of neoplastic involvement denoting inoperability. The finding of carcinoma cells in the pleural fluid establishes the diagnosis. They were found in seven of the 38 cases with pleural fluid. None of the 38 cases was operable. Neoplastic cells may occasionally be found in the sputum.

Finally if all other means fail to establish a positive diagnosis and roentgenological evidence is sufficiently strong, there being no obvious metastatic lesions or other contraindications, exploratory thoracotomy should be done. It is a relatively safe procedure and carries a low mortality and morbidity rate. The average stay in the hospital is less than two weeks, comparable to exploratory laparotomy. Direct examination by both palpation and inspection is possible and tissue can be removed for frozen section diagnosis if necessary. *Since early resection is the only hope of cure the slight risk of the thoracotomy is not to be compared with the hazard of waiting for a positive diagnosis which may only come in the form of a hopeless metastatic lesion.*

Treatment

There is, at the present time, a complete unanimity of opinion that the only curative treatment of bronchiogenic carcinoma is complete removal of the cancerous tissue, together with all involved or suspicious mediastinal lymph nodes. Total pneumonectomy rather than lobectomy is usually recommended as it is the best means whereby one can be assured of remov-

ing all regional nodes. Usually there is no choice as in the majority of cases the location of the bronchial lesion demands it. Occasionally emphysema in the contralateral lung and dypsnea make a lobectomy advisable, if it is technically possible. In such cases the risk of recurrence is probably not as great as the possibility of having a respiratory cripple as the end result. Ordinarily the remaining lung shows a great capacity for the necessary compensatory changes and only one patient in the living group is suffering from more or less disabling dyspnea. Lobectomy has been performed on four patients in this series of cases.

Roentgen-ray therapy, except for palliative reasons in the inoperable or non-resectable cases, is mentioned only to be condemned. It does not cure and the feeling of well being and improvement following its use usually causes the patient to postpone a possible curative operation until the lesion has reached a prohibitive stage.

Present day operative mortality is relatively low, 5 to 20 per cent, and the final results of this and other reported series of cases attest to the value of pneumonectomy for an otherwise 100 per cent fatal disease. Seventeen patients or 39.5 per cent lived for from two months to three and a half years. Thirteen patients or 30.2 per cent are alive from two years to seven years post-operatively. All are in good health except one of the lobectomy patients who has had a recurrence.

The true value of any surgical procedure is not reflected in, and should not be judged by, the immediate operative mortality. A very low early and late surgical mortality rate can be obtained by accepting for resection only those patients who have early lesions and who are in good condition, thus condemning to certain death many who might otherwise be cured. To quote Graham,[6] speaking of the dilemma of the thoracic surgeon, "Shall we offer a chance to the bad risk victim of bronchiogenic carcinoma, even if it is only a small one, to be cured of his otherwise hopeless condition, or shall we decline to operate because of the great danger of an operative mortality?"

Summary and Conclusions

A careful analysis of 231 proved cases of bronchiogenic carcinoma is presented. Only 77 of this group were considered operable and in only 43 of these 77 was resection possible. Seventeen or 39.5 per cent of the resected cases lived for from two months to three years post-operatively and 13 or 30 per cent are alive from two to seven years after operation.

The majority of patients do not seek medical aid for three or more months after the onset of symptoms and in over 50 per cent of the cases there is a delay of six or more months in establishing the diagnosis. Until the avoidable delays in diagnosis are overcome there can be little chance of increasing the present relatively small number of possible cures of lung cancer. The optimum time of operation is within six months of the onset of significant symptoms. This does not mean that it is safe to delay opera-

tion for as long as six months. Operation should be performed *as soon as* a tentative or actual diagnosis can be made. Routine chest roentgen-rays are essential to an early diagnosis of the peripheral type of lesion which usually presents no early symptoms. The squamous cell type offers the best prognosis.

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REHABILITATION: WARTIME LESSONS APPLIED TO PEACETIME NEEDS *

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THE service convalescent training program was born of necessity. With a general shortage of time and men in the early days of 1942, it was not feasible to wait for leisurely indolent convalescence and the time necessary for nature to take its course. The original program was started at Jefferson Barracks, Missouri in November 1942 after the great need was emphasized by Brigadier General Hugh Morgan on one of his early inspection trips.

Designed originally for the pre-combat sick or injured soldier, the program had a dual mission: first, to send the soldier-patient back to duty in the best possible physical condition in the shortest possible time; second, to teach the soldier-patient something that would make him a more efficient and more effective fighting man. With the inception of this program, physical activity and military education became as much a doctor's prescription as drugs and diet. The results achieved proved so successful in the experimental phase of the program that in December, 1942 such a program was initiated in all Army Air Forces hospitals.

The classroom and gymnasium were moved into the wards for it was noted early in the convalescent program that to obtain maximum results, reconditioning should start as early as possible following acute disease or injury, and the program had to be purposeful, progressive, and graduated to the individual patient's physical tolerance.

In order to make the soldier-patient a member of the therapeutic team, the HANDBOOK OF RECOVERY (AF Manual No. 23) [1] was prepared as a prescription blank for all types of orthopedic disabilities. It included a nine-page section on anatomy, physiology and pathology written in simple language to show the soldier-patient why he was in the program, the value and effects of active exercise, how bones, muscles and nerves are made, what happens when they are injured and how they heal. This was followed by a series of two-page prescription blanks for the specific injury demonstrating to the soldier-patient by diagram the normal function of the injured part, his diagnosis and disability, the type of physio-therapy necessary, the illustrated active exercises to be done with and without supervision, and a personal objective recovery chart which the patient himself maintained. This was an effective innovation as it not only gave the patient an insight into and understanding of his condition, but great motivation through his ability to measure his own progress objectively.

LET'S WALK (AF Manual No. 49) [2] was another publication designed for the patient which met with widespread use and approval. Unique in its

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presentation, this booklet dealt with the functional aspects of walking with the use of aids. It first gave the patient a brief psychological orientation to his disability and then proceeded to demonstrate objectively through the use of illustrations and charts the factors involved in walking with aids.

Some of the pertinent observations made on the results of the Convalescent Training Program after three years of experience were: hospitalization time was shortened; hospital readmissions were reduced; sick leaves were eliminated except in extraordinary cases; and the morale of the soldier-patients was immeasurably improved when they were kept busy and interested in purposeful activity.

A number of interesting clinical studies were made. Van Ravenswaay [3] and his co-workers studied 645 cases of virus pneumonia treated in the same acute ward. These cases were later assigned to alternate convalescent wards. In Ward I "nature was allowed to take its course" and men sat around until they and the medical officer felt they were ready for duty. In Ward II the patients were kept in bed until their sedimentation rate reached 10 mm. in one half-hour and then were put in a reconditioning program, beginning with exercise for one-half hour the first day and increasing progressively until the twelfth day when the patient was participating in a full five-hour day of physical training, mass games, competitive sports and active recreation including a ten mile hike. Group I averaged 45 days' hospitalization with a 30 per cent recurrence rate. The patients in Group II averaged only 31 days with but a 3 per cent recurrence rate.

Karpovich [4] and his associates at the School of Aviation Medicine, San Antonio, Texas, studied a similar group of 200 aviation cadets convalescing from virus pneumonia. Using a modification of the Harvard Step Test and starting as early as the first afebrile day, Karpovich found that by the reactions to this test it was possible to determine, with some degree of accuracy, the patient's ability to enter into and participate in an active convalescent program. An interesting by-product of Karpovich's work was the observation that patients undergoing the tests required five days less hospitalization time than those participating in the general program. These findings were suggestive of the ability of the convalescent to participate in an even more active program with beneficial results.

Early in the operation of the convalescent program it was noted clinically that orthopedic patients requiring fixation of a specific member did not, if kept in top physical condition generally, show the usual degree of muscular atrophy in the fixed part and when the cast was removed could be reconditioned to duty in approximately one-half the usual convalescent time. Whether this was due to increased blood velocity, exercise within the cast, vasomotor stimulation, or lack of capillary loss gives food for thought and further investigation.

As a part of the AAF Rheumatic Fever Control Program, Karpovich, Weiss, Starr and Ershler [5] carried out a study on physical fitness testing and physical training of convalescent rheumatic fever patients. Because of the

chronic, recurrent nature of the disease and the possibility of disabling cardiac sequelae, it was felt that special emphasis should be placed on the standardization of physical activity and convalescent training of these patients by working out a series of graduated physical fitness tests which could be used, in conjunction with the usual clinical observations, to determine the rate at which the patient could safely be permitted to progress to increased physical activity. The details of this study are available in the original report. It is interesting to note, however, that there were no recurrences or untoward reactions in any patient participating in the study.

Reports on the effects of bed rest have been detailed in the literature,[6, 7, 8, 9] and special studies have been made by Keys [10] and Barr [11] and his associates. Reports on the effects of early ambulation in surgical patients have been made by Powers [12] and Whipple,[13] and their significant observations are most pertinent in evaluating the management of convalescence.

To meet the needs of overseas combat casualties special convalescent hospitals were activated in 1943. These hospitals were designed to meet the needs of the whole man regardless of what those needs were—medical, physical, psychiatric, social, vocational, educational or personal. The physical reconditioning program emphasized competitive team play and active recreation. The educational program consisted of training in military specialties. This combined emphasis on both physical and educational training provided the diversional media through which, with the aid of personal counseling and psychological readjustment, resocialization of the individual patient was achieved. The purpose of the program was to provide the soldier-patient with a laboratory of opportunity through physical reconditioning, educational-avocational pursuits and recreation whereby he might recover the attitudes, habits, and values compatible with normal behavior patterns.

In the convalescent hospital each patient was assigned to a designated "personal physician." This personal physician was carefully chosen because of his training, experience and ability to understand and evaluate the problems of the patient. Many physicians were given special clinical courses in the newer psychiatric, diagnostic, and therapeutic technics. They were in reality specialists in the psychology of emotional stress and the sciences of organic repair.

After a thorough evaluation of a patient's disability, the personal physician was ready to turn to the team of ancillary specialists for specific corrective measures in the fields of physical, medical, educational, occupational and recreational therapy. He served as a coördinator in integrating the work of these specialists in their coöperative efforts toward restoration of the normal physical and functional being of the whole man.

The rehabilitation programs of the armed forces have demonstrated what can be done for the physically and emotionally wounded and handicapped to make them self-sufficient, self-respecting, self-supporting persons.

Both the medical profession and the general public are genuinely con-

cerned with the problem which must be faced by thousands of our disabled veterans as they return to their communities. These men have earned and deserve the best that a grateful nation can give them, but few of us realize that in comparison to the total numbers, our disabled veterans constitute only a small part of the handicapped and disabled we have in this country.

We had in 1940 in the United States some six and one-half million disabled males between the ages of 15 and 64 years, men who normally would be income-producing. These six and a half million, plus the number of disabled or handicapped veterans being discharged from our military hospitals will give us, when demobilization is completed, approximately eight million working age males who are disabled to the extent of requiring physical or vocational rehabilitation or special placement aids, if they are to be successfully employed. This represents one person in sixteen in our general population, and one in seven in our male working population. The number of persons who are permanently disabled by accident alone increases by 350,000 each year. The total problem has been summarized by Donahue and Tibbitts.[14]

During the first four years of war there were approximately 17,000 amputations in the Army, but during this same period there were 120,000 major amputations necessitated by disease or accident in our civilian population.

The armed forces and some outstanding community and civilian agencies, such as New York's Institute for the Crippled and Disabled, have demonstrated that the physical and emotional rehabilitation of our handicapped and disabled is possible. Some authorities have estimated that up to 97 per cent of all our handicapped can be rehabilitated to such an extent that they can be gainfully employed.

The short labor market during the war gave many disabled persons the first opportunity of their lives to take a place on the production line and prove that they could, with good selective placement, produce on a par with the normal workers. An example is the Ford Motor Company River Rouge plant where more than 11,000 handicapped civilian workers were employed.

During the war 83 per cent of our nation's industries employed handicapped workers. Those industries have reported that among the handicapped there has been a much smaller labor turnover, less absenteeism, fewer accidents and equal or higher production rates. Many employers before this vast experience with handicapped employees, had a fear of increased accident rates. The industrial accident rate of 87 of the great industrial plants in America, each having from 200 to 12,000 handicapped employees, has disproved that conception.

The answer to the utilization of handicapped workers lies not so much in "fitting the job to the worker" as in "fitting the worker to the job." Through this procedure the worker in reality becomes non-handicapped as far as his particular job is concerned.

Most individuals use less than 10 per cent of their potential efficiencies in

normal pursuits. It is only in emergencies that we called upon our tremendous reserves of physical power and ability. In many cases a worker's physical defect acts as a tremendous stimulus to over-compensation, resulting in extraordinary physical ability. Adler [15] developed a complete system of psychology on the basis of inferiority. The employer of handicapped workmen is putting that psychology into purposeful and gainful application.

The National Office of Vocational Rehabilitation has reported how rehabilitation pays off economically.[16] Of the 43,997 persons undergoing vocational rehabilitation under this agency in 1944, 22 per cent or more than 10,000, had never been gainfully employed. The average annual wage of the entire group prior to rehabilitation was $148. After rehabilitation, the average annual wage of the group increased to $1,768. The total earnings of the entire group rose from $6,510,556 to $77,786,696.

Prior to rehabilitation the majority of these persons relied on general public assistance. The annual cost of this assistance to the taxpayer was from $300 to $500 per case, but the total cost of their rehabilitation averaged only $300 per case, a non-recurring expenditure.

No degree of economic gain, however, can measure the social and moral satisfactions obtained by the successfully rehabilitated and employed handicapped worker and his family. Nor can it measure the value to society in the transformation of these individuals from dependents to productive, self-reliant individuals.

The question usually raised is, "If the vocational rehabilitation program has been so successful, why isn't it extended to meet the needs of the entire nation?" The answer is simply that the rehabilitation centers to which these cases can be referred do not exist. The funds and authority are available, but the facilities for doing the job are inadequate. Several national organizations are making efforts to stimulate public interest in rehabilitation by demonstrating to both the medical profession and the public what actually can be done by an integrated rehabilitation program.

The Baruch Committee on Physical Medicine has recently published a report [17] translating the experience of the armed forces into civilian application in order that this experience may be made available to the medical profession and those interested in community rehabilitation centers. They are blueprinting a model center, outlining its mission, organization, components, physical set-up, approximate cost, and its relationship to the medical and allied professions—industry, labor, social, and governmental agencies —and to the community as a whole.

Rehabilitation is primarily a medical problem and our responsibility does not end when the discharge note is made on the hospital chart. Disease cannot be divorced from the problems of personality, economy, and social adjustment.

The retraining of the paraplegic and the hemiplegic is just as important as the medical management. The cardiac and the arthritic often need vocational or avocational readjustment just as badly as they need medication.

The attitudes of the chronic invalid can change entirely with the simplest routine of productive activity.

Utilizing the experience of the armed forces, civilian hospitals can be made into institutions of opportunity. Surveys have shown that the average patient in the hospital spends 10 per cent of his time in pain and 90 per cent in boredom. There is real need for dynamic hospital programs designed to aid the convalescent patient in his orientation back to normal living. Classes in dietetics, pre-natal care, home nursing, consumer buying, and home economics can be combined with forum discussion groups, craft courses designed especially for the homebound, and programs which are aimed to promote a better understanding of our new responsibility as citizens in a global world. Special training films on various industrial projects, travel, vocational information, and films of historical and scientific interest are available without cost from numerous sources. With such a convalescent program this phase of hospitalization could be transformed from one of boredom to one of opportunity.

A recent survey made in a large general hospital revealed that 5 per cent of the general surgical patients, 15 per cent of the medical patients and 85 per cent of the orthopedic patients were in need of no further definitive care but were in need of rehabilitation and retraining in order to go back to work. Thirty per cent of all patients visiting the medical and surgical out-patient clinic were in the same category. Thousands of critically needed hospital beds could be made available, with great advantage to the patient, if rehabilitation and convalescent facilities were available.

Specialized rehabilitation centers must be established to serve the severely handicapped, to furnish the third phase of medical care that takes the patient from the bed back to productivity. This is a medical responsibility —a medical necessity—if we are to fill the existing gap in the complete care of the patient.

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PENICILLIN IN THE TREATMENT OF NEUROSYPHILIS. IV. CEREBROSPINAL FLUID CHANGES IN CASES OF SYMPTOMATIC NEUROSYPHILIS *

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A study of the effect of penicillin in various forms of neurosyphilis was begun at the Johns Hopkins Hospital in October 1943. The results of the first two years' experience are being reported in a series of papers. The first of these [1] dealt with the treatment of asymptomatic neurosyphilis, the second [2] with general paresis, and the third [3] with Erb's spastic paraplegia. The present paper, the fourth of the series, is concerned with the changes in the cerebrospinal fluid abnormalities in various types of symptomatic neurosyphilis considered as an admittedly conglomerate whole.

Although there are disadvantages in grouping together such widely divergent entities as general paresis, tabes dorsalis, meningovascular neurosyphilis and Erb's spastic paraplegia, the amalgamation is justified by the fact that all have in common *T. pallidum* as the causative agent and specific abnormalities in the cerebrospinal fluid.

The clinical evaluation of the results of therapy in cases of neurosyphilis is subject to two difficulties: (1) clinicians vary in their backgrounds, in their special interests and in their interpretations not only of subjective but also of objective phenomena; and (2) because neural tissues, once destroyed, do not regenerate, it is not infrequently debatable what proportion of residual neurologic or psychiatric abnormalities is due to treatment failure and what proportion is due to irrevocable pre-treatment tissue destruction. These are considerations which make it a matter of extraordinary difficulty to evaluate clinical results of treatment.

The spinal fluid abnormalities are, on the other hand, objective and unequivocal criteria which may be analyzed quantitatively without qualification of the raw data.

These considerations have led such a careful neuropsychiatric observer as Dattner [4] to the opinion that the efficacy of any form of treatment in neurosyphilis should be determined by the response of the cerebrospinal fluid and not by clinical data.

Case Material

As of January 1946, 149 patients with various clinical manifestations of neurosyphilis have been treated with penicillin. Forty-one of these patients

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This study was made under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and The Johns Hopkins University.

had general paresis; 13 were considered to have taboparesis; 45 had either tabes dorsalis, primary optic atrophy, or both; 19, meningovascular neurosyphilis; six, Erb's syphilitic spastic paraplegia; and 25 patients herein "unclassified" had in most instances pupillary abnormalities only.

One hundred and eleven of these patients were treated with penicillin alone, in amounts ranging from 2.0 to 10.0 million units in divided doses; the remaining 38 patients received from 2.0 to 6.0 million units of penicillin in divided doses concurrently with induced tertian or quartan malaria.

The sodium salt of commercial penicillin was used throughout. The preparations used were those of several manufacturers and of many lot numbers. The composition in terms of the now identified penicillin fractions,

TABLE I

Summary of Case Material: Diagnosis, Race, Sex, and Age, and Cerebrospinal Fluid Grouping in Terms of Degree of Abnormality

Diagnosis	Cases	Race and Sex				Age							CSF Group			
		W.M.	W.F.	C.M.	C.F.	10–19	20–29	30–39	40–49	50–59	60–69	70–79	Normal	I	II	III
Tabes Dorsalis and Primary Optic Atrophy	45	20	8	16	1	1	2	15	19	4	1	3	2	0	16	27
General Paresis	41	23	6	11	1	1	5	12	15	3	5	0	0	0	0	41
Tabo-Paresis	13	8	2	3	0	1	0	4	6	2	0	0	0	0	2	11
Meningovascular Neurosyphilis	19	4	2	10	3	0	3	9	7	0	0	0	0	0	2	17
Erb's Spastic Paraplegia	6	3	1	2	0	0	0	1	3	1	1	0	0	0	3	3
Unclassified Neurosyphilis	25	5	2	9	9	1	4	9	9	2	0	0	1	0	6	18
		63	21	51	14	4	14	50	59	12	7	3	3	0	29	117
Totals	149	84		65												
		149				149							149			

G, F, X, and K, is unknown. Aqueous solutions were injected intramuscularly every three hours, day and night. Individual doses ranged from 40,000 to 50,000 units; the total number of injections, from 50 to 200. Intrathecal therapy was not employed. Those treated with malaria inoculata were allowed to have from eight to 12 paroxysms, and approximately 40 hours of fever in excess of 104° F. Penicillin was usually begun at the time of the first apparent malarial fever.

A summary of the case material upon which this study is based is given in tables 1 and 2. Included in the group were 114 male and 35 female

TABLE II

Summary of Case Material: Diagnosis, Penicillin Plus Malaria vs. Penicillin Alone, Penicillin Dosage, Duration of Symptoms, and Cumulative Duration of Follow-Up Observation

Diagnosis	Cases	Duration of Symptoms (in months)					Penicillin plus Malaria	Penicillin alone	Penicillin Dosage (in millions of units)			Cumulative Duration of Follow-Up Observation (in weeks)									
		Less than 6	6–12	12–24	More than 24	Unknown			Less than 4.0	4.0–8.0	More than 8.0	0	1–4	10–19	20–29	30–39	40–49	50–59	60–79	80–99	100–120
Tabes Dorsalis and Primary Optic Atrophy	45	9	9	2	11	14	13	32	8	19	5	45	42	34	32	29	25	20	12	4	0
General Paresis	41	16	9	8	7	1	17	24	2	13	9	41	40	37	26	17	11	8	5	4	4
Tabo-Paresis	13	2	4	1	6	0	7	6	5	1	0	13	13	12	12	10	8	7	5	5	2
Meningovascular Neurosyphilis	19	9	4	0	4	2	1	18	1	17	0	19	19	18	12	11	10	9	8	0	0
Erb's Spastic Paraplegia	6	2	0	1	3	0	0	6	2	2	2	6	6	5	4	3	1	1	1	1	0
Unclassified Neurosyphilis	25	0	0	0	3	22	0	25	2	23	0	25	25	23	15	14	13	10	6	2	1
Totals	149	38	26	12	34	39	38	111	20	75	16	149	145	129	101	84	68	55	37	16	7
		149					149		111												

patients; 84 whites and 65 Negroes. The mean age of these patients was 43.6 years, the youngest being 10, the eldest 79 years.

Using Moore's [5] classification, by far the greatest number of pretreatment spinal fluids were Group III, with increased cell count, elevated spinal fluid protein, strongly positive Wassermann reactions, and "first zone" colloidal mastic tests. Twenty-nine spinal fluids were classified as Group II, or intermediate in degree of abnormality; none as Group I. Three spinal fluids were normal at the time treatment was instituted.

Thirty-six patients (24 per cent) had had a recent onset of symptoms, i.e., less than six months. In 64 (43 per cent), the first symptoms had been present for less than one year prior to admission. The duration of symptoms was unknown in 39 cases, including almost the entire group of patients with "unclassified" neurosyphilis.

Seventy-one had received some previous antisyphilitic therapy: 11 malaria plus chemotherapy, 60 varying amounts of arsenical and bismuth chemotherapy alone. In no case had malarial therapy been given within a year prior to the institution of penicillin therapy. In only seven of the patients previously treated had any improvement been apparent; all of these but two having received malaria. No patient markedly improved from any previous treatment was treated with penicillin.

Effects of Therapy

The overall effect of treatment upon the spinal fluid abnormalities (cell count, total proteins, colloidal mastic, Wassermann reactions) is shown in figure 1.

Cell Count and Total Proteins: Following treatment with penicillin alone or with penicillin plus malaria, the pleocytosis of the cerebrospinal fluid almost invariably became normal. This was a prompt, and during the period of observation, generally a well-sustained effect.

A similarly favorable and almost as prompt effect upon the total proteins of the cerebrospinal fluid was apparent.

Applying the Dattner-Thomas [4] concept of "activity," as judged by increased cell counts and total proteins, there were nine patients with evidence of an "active" process in the central nervous system six or more months after treatment. Of these, three had general paresis, one tabes, two taboparesis, one Erb's spastic paraplegia and two unclassified neurosyphilis. Since 96 patients have been under observation for six or more months, 9 per cent of those followed for that length of time had evidence of activity six months or more later. One of these is known to have become normal subsequently without further antisyphilitic therapy.

Colloidal Mastic Test: In analyzing the results of treatment upon abnormalities in the colloidal mastic test, an artificial statistical device has been utilized. The arithmetic sum of the arbitrarily assigned readings of the first three tubes was used. Thus, a colloidal mastic of *554*321000 would be recorded as 14, and one of *221*11000000, as 5.

It is evident from figure 1 that penicillin therapy favorably influences the results of the colloidal mastic test. It also is apparent that this effect, while neither as prompt nor, during the observation period, as complete as in the case of the cell count and total protein, was similarly well sustained. There was no case followed for more than one year in which some improvement in the results of this test had not occurred.

Spinal Fluid Wassermann Test: The statistical concept of reciprocal relationship was utilized in analyzing the effects of therapy upon the cerebrospinal fluid Wassermann titer. In our laboratory, the spinal fluid

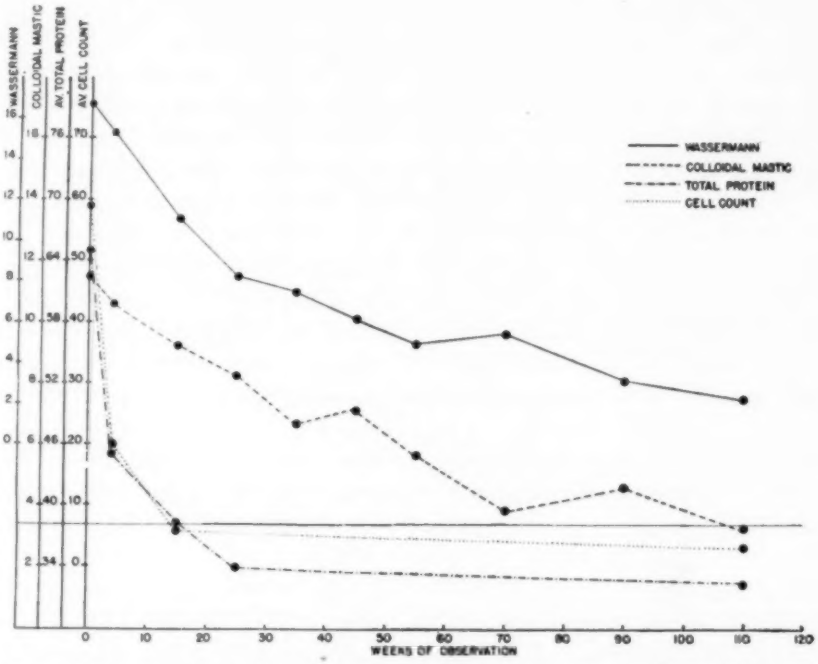

FIG. 1. Changes in fluid abnormalities following treatment with penicillin or penicillin plus malaria.

Wassermann is quantitated by the use of decreasing amounts (1.0, 0.8, 0.6, 0.4, 0.2, 0.1, 0.05, 0.03 and 0.01 c.c.) of spinal fluid, and the result recorded as the minimal quantity necessary for complete fixation of complement. The following arbitrary reciprocal values were assigned to the several readings: 0.01–100; 0.03–33; 0.05–20; 0.1–10; 0.2–5; 0.4–2.5; 0.6–1.6; 0.8–1.2; 1.0–1.0; negative –0. The mean of the reciprocal is the basis for the graphic analyses of this paper.

Therapy with penicillin or with penicillin plus malaria was found to lower gradually the average Wassermann titer of the cerebrospinal fluid of this group of patients with asymptomatic neurosyphilis.

The favorable effect, perhaps even more than that noted upon the results of the colloidal mastic test, was of slow evolution. It was, however, equally

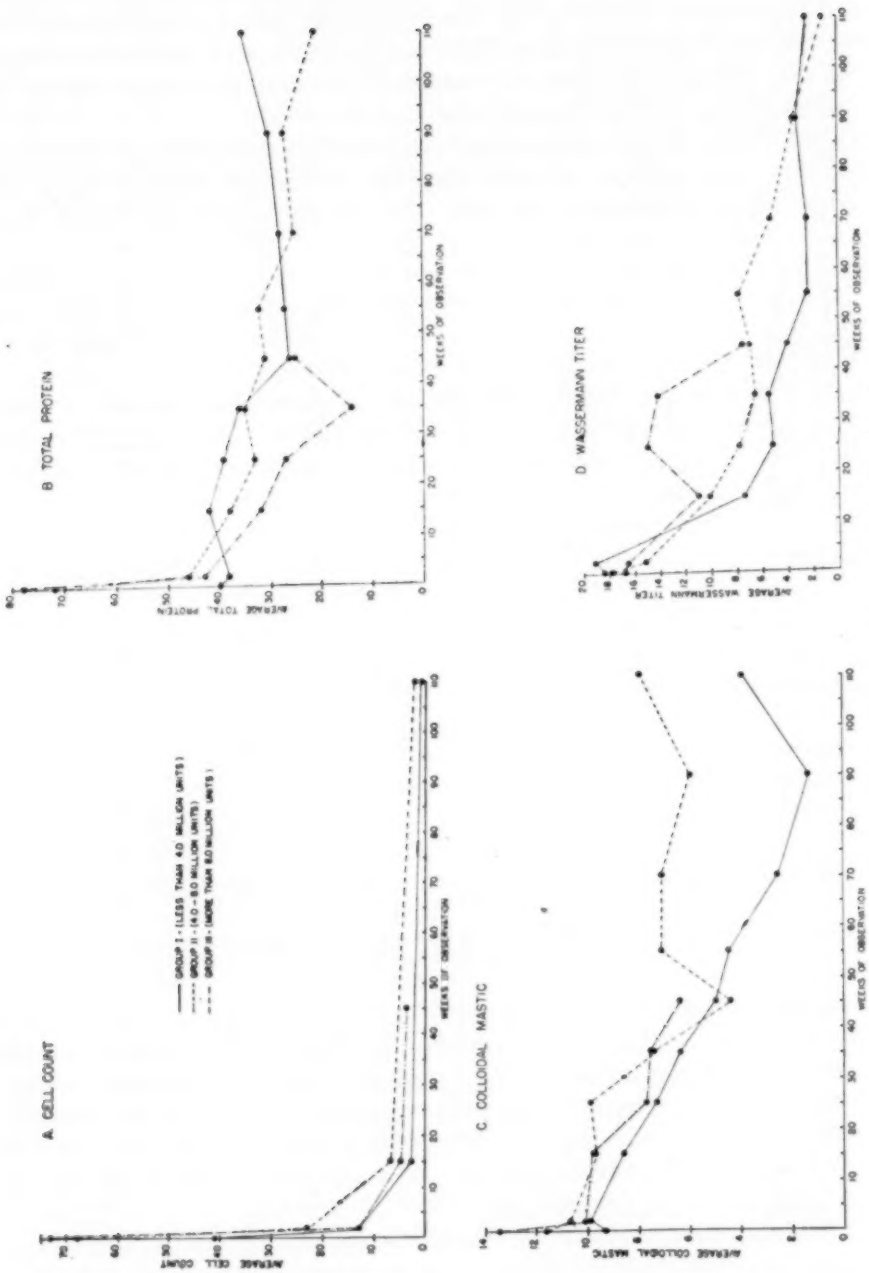
A. CELL COUNT
B. TOTAL PROTEIN
C. COLLOIDAL MASTIC
D. WASSERMANN TITER
GROUP I - (LESS THAN 4.0 MILLION UNITS)
GROUP II - (4.0 - 8.0 MILLION UNITS)
GROUP III - (MORE THAN 8.0 MILLION UNITS)
WEEKS OF OBSERVATION

FIG. 2. Effect of penicillin dosage (penicillin alone).

well sustained. All but five (of 53) patients (two with tabes, three with unclassified neurosyphilis) who were followed for one year or more, have shown some decrease in the spinal fluid Wassermann titer.

Factors Influencing the Results of Treatment

1. *Penicillin Dosage:* The optimal dosage of penicillin in the treatment of neurosyphilis is not known. None of the patients in this study received more than 10 million units. In evaluating the effect of penicillin dosage, only those 111 patients treated with penicillin alone were considered.

A comparison of the results of treatment with less than 4.0 million units (Group I), 4.0 to 8.0 million units (Group II) and with more than 8.0 million units (Group III) is shown graphically in figure 2. Analysis of these data shows no distinct advantage in the use of larger doses. In the light of recent information [6] which indicates that the composition of commercial penicillin was changing during the period of this study, no conclusions can be drawn from this observation.

2. *Duration of Symptoms:* In the second paper of this series, it was pointed out that although in patients with general paresis there was no significant effect of the duration of symptoms upon the response of the spinal fluid cell count, total proteins or colloidal mastic test, the spinal fluid Wassermann did become less strongly positive, more rapidly and to a more significant degree, among patients whose symptoms were of less than one year's duration.

When all cases of neurosyphilis are considered as a single conglomerate group, no significant effect of duration of symptoms upon any of the spinal fluid abnormalities, including the Wassermann, can be demonstrated (figure 3).

3. *Extent of the Cerebrospinal Fluid Abnormalities:* Although the vast majority (117 of 149) of the initial spinal fluid examinations in this group of patients are classified as Group III (Moore), it seems desirable to ascertain whether the extent of the cerebrospinal fluid abnormalities at the time treatment was started influences the response to therapy.

The data shown in figure 4 indicate that the spinal fluid changes approach normality at about the same rate no matter how extensive they may have been at the time therapy was instituted. Lesser degrees of adventitiousness fade into the normal range in a shorter period of time than do those more extensive, but apparently only because the initial degree of severity was less removed from the norm.

4. *Penicillin Alone vs. Penicillin plus Malaria:* In general, it may be stated that the spinal fluid response to therapy was more striking in the group of patients treated with concurrently administered penicillin-malaria treatment than among those treated with penicillin alone.

Study of figure 5 reveals little difference between the two groups in respect to the immediate effects upon the cell count or total proteins. In

Fig. 2. Effect of penicillin dosage (penicillin alone).

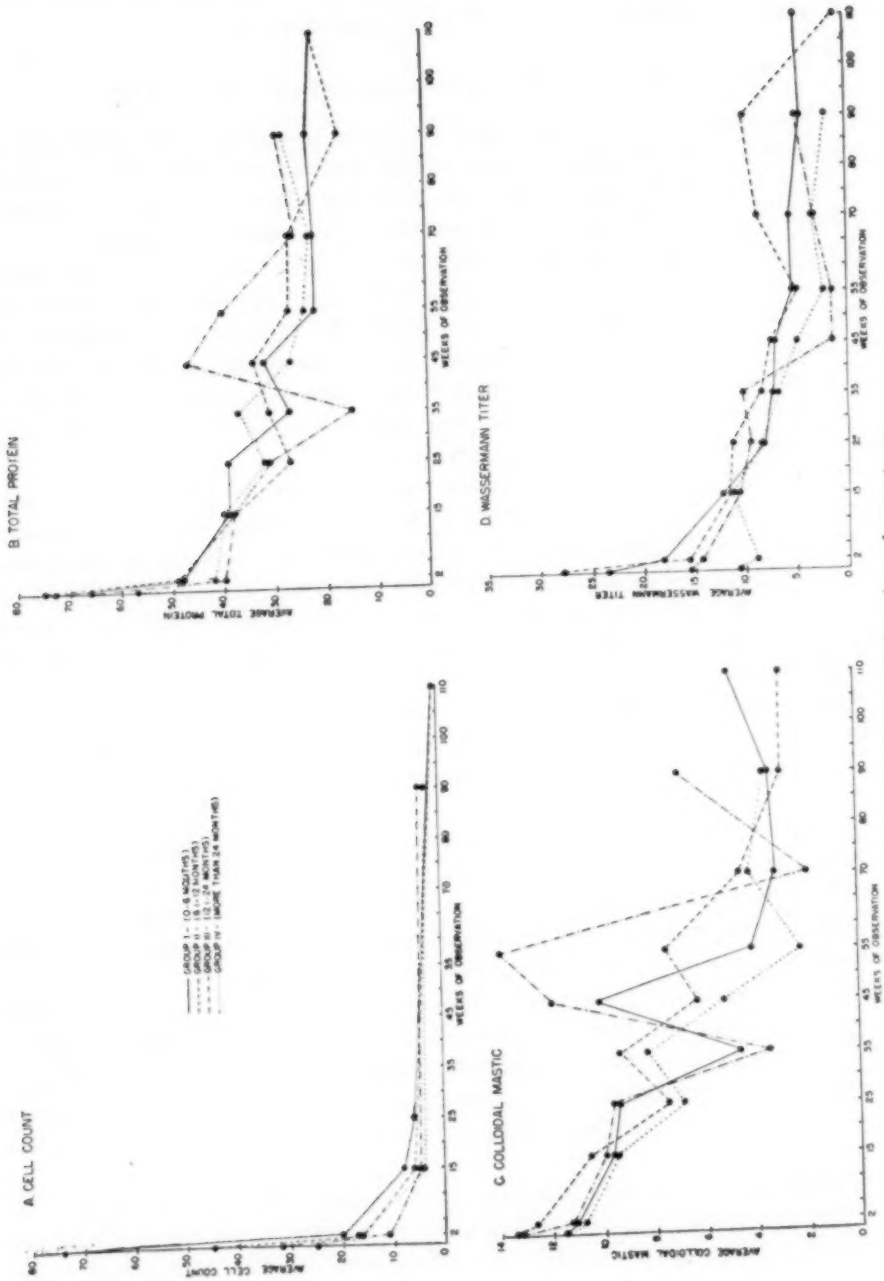

FIG. 3. Effect of duration of symptoms.

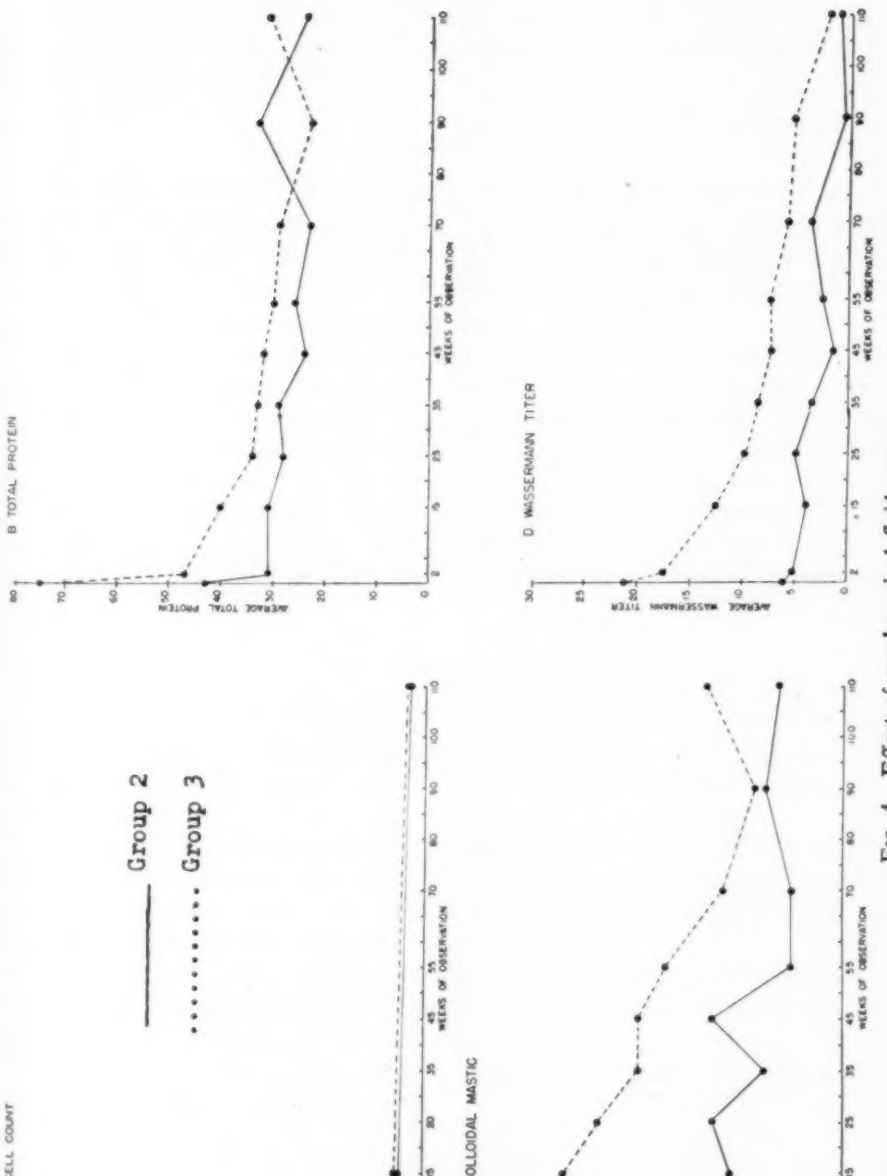

FIG. 4. Effect of cerebrospinal fluid groups.

FIG. 3. Effect of duration of symptoms.

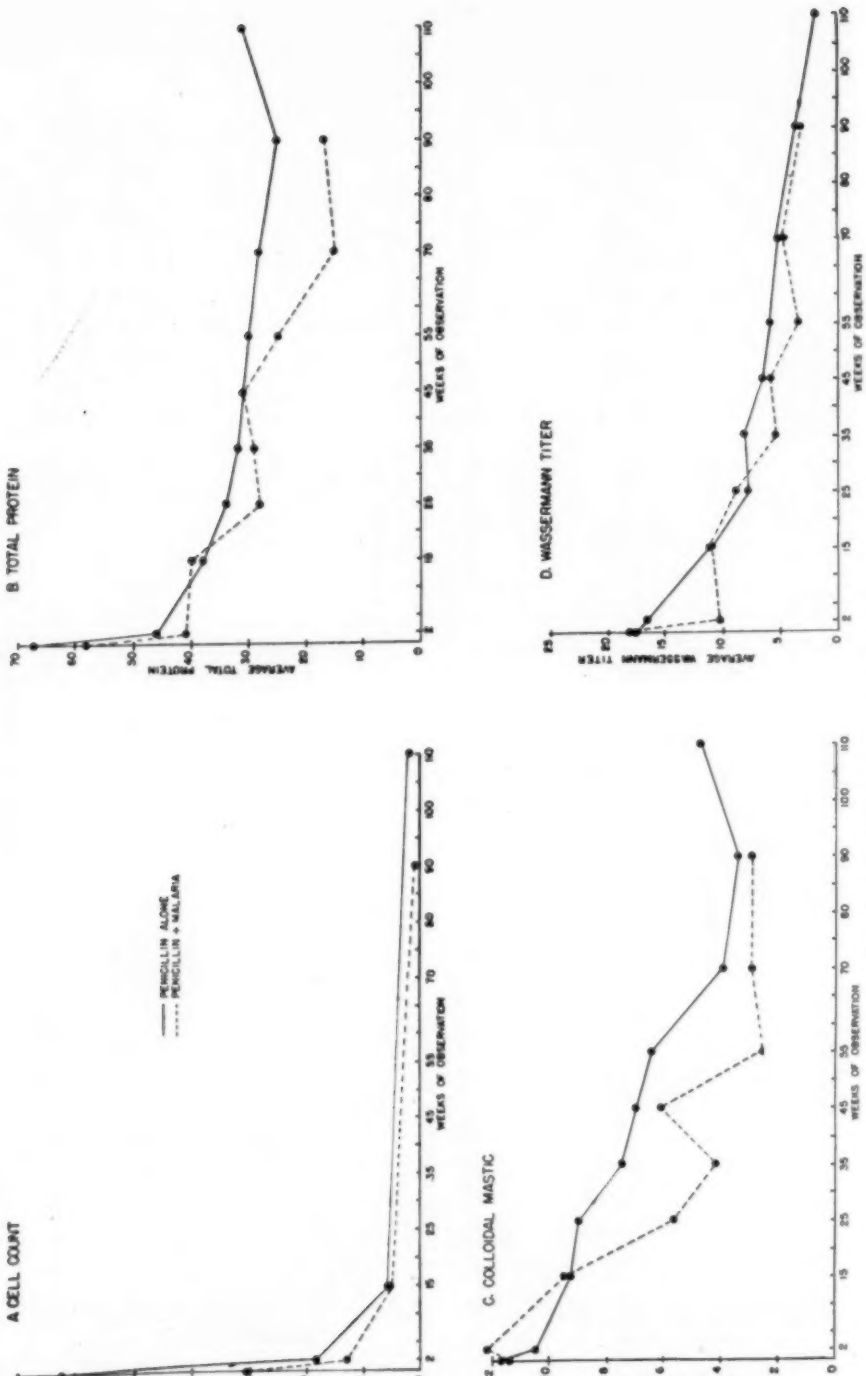

FIG. 5. Penicillin alone vs. penicillin plus malaria.

both groups, the response was prompt, almost invariably complete and generally well sustained.

Considering the colloidal mastic test and the Wassermann titer in the cerebrospinal fluid, there appears to be some evidence at least that concurrent penicillin-malaria is superior to penicillin alone.

Discussion

Although there are definite disadvantages in considering as one the several forms of neurosyphilis, varying as widely as acute meningovascular syphilis and chronic Erb's spastic paraplegia, we have sought thereby to arrive at some conclusions as to the overall effect of penicillin upon the spinal fluid of patients with neurosyphilis.

Many important questions cannot be answered fully as yet: the precise mode of action of penicillin in syphilis of the central nervous system; the optimal time-dose relationship; whether penicillin ultimately will replace entirely malarial therapy; and perhaps most important of all, the ultimate outcome for these patients in terms of years of observation. However, the improvements noted in the various cerebrospinal fluid abnormalities indicate, and clearly, we believe, that penicillin is a valuable addition to the therapeutic armamentarium in the management of patients with neurosyphilis.

Summary

1. One hundred and forty-nine patients with various clinical manifestations of central nervous system syphilis have been treated with penicillin. Of these, 111 received penicillin alone, and 38 penicillin concomitantly with malarial therapy.

2. Improvement in the spinal fluid abnormalities generally was apparent. As a rule, the cell count and total proteins promptly became and remained normal. Colloidal mastic and Wassermann tests gradually improved, the improvement being well-sustained.

3. The degree and rapidity of improvement could not definitely be correlated with (a) the penicillin dosage; (b) the duration of symptoms; nor (c) the extent of the spinal fluid abnormalities.

4. More favorable results followed therapy with penicillin plus malaria than treatment with penicillin alone.

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Fig. 5. Penicillin alone vs. penicillin plus malaria.

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THE MANAGEMENT OF INFECTIOUS HEPATITIS *

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Introduction

During the last five years the incidence of infectious hepatitis has approached epidemic proportions among both civilians and military personnel in various parts of the world.[1, 2] The opportunity thus offered for intensive study has led to a better understanding of the nature of the disease and to certain radical changes in our point of view towards it.[2, 3] It has become apparent that infectious hepatitis may have more serious consequences than was thought in the past. Thus proper treatment assumes increased importance which is further enhanced by the demonstration that it can significantly influence the course of the disease and the prognosis. Although some of our observations have already been published [2, 3] the importance of this problem warrants a more detailed discussion than has previously been presented.

Material and Methods

Our experience, gained largely in the army, is based on a systematic study of over 2000 cases of infectious hepatitis both in this country and in the Mediterranean Theater and the observation of some 6000 more. This material and the methods employed have been previously described.[2, 3] It is important to emphasize that this was a planned study and not simply a review of case records. For the evaluation of therapy, comparable groups of a single type, either acute hepatitis with jaundice, acute hepatitis without jaundice or chronic hepatitis of over three months' duration, were employed. Proper control studies were made of all laboratory and clinical procedures.

The Seriousness of the Disease

Since the seriousness of a disease is perhaps the most important factor in determining the need for careful or extended treatment, it is pertinent to examine the relevant evidence regarding infectious hepatitis.

Mortality Rate. Although the mortality rate during the acute stage has usually been low, varying between one to three cases per thousand, mismanagement and various complicating factors can markedly increase the risk. Thus Snell [4] has reported an 18 per cent mortality in a series of 32 consecutive cases.

Duration of the Disease. The duration of disability and of evidence of liver disease is prolonged. In our experience the period from onset of

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symptoms to reasonably complete symptomatic and clinical recovery averages about two months. Although under the best conditions the majority of patients should be well in six weeks, about 10 per cent will still be sick after three months. Laboratory evidence regarding the duration of liver disease is shown in table 1. During the third month after onset of symptoms 71

TABLE I

Findings in 180 Consecutive Cases of Acute Infectious Hepatitis during the Third Month Following Onset

Bromsulfalein (5 mg./kg.)	
Total cases tested	122
Normal	29%
3–4% dye retention in 1 hr.	20%
5–9% dye retention in 1 hr.	36%
10% plus dye retention in 1 hr.	14%
Cephalin cholesterol flocculation test	
Total cases tested	142
Normal	64%
1+ or 2+ in 24 hrs.	20%
3+ or 4+ in 24 hrs.	15%

per cent showed an abnormal bromsulfalein dye retention and in many of these this test was strongly positive. On the basis of present knowledge about one half of these patients failed to receive the best treatment but it was probably quite as good as that which the average case received before the war. Finally, the duration is substantiated by the persistence of histological evidence of inflammation.[5, 6]

Residuals. Residuals and sequelae are not uncommon and are of several sorts. The condition that we have described under the term "chronic active hepatitis" [3] which is characterized by intermittent periods of disability for months or years develops in from 5 to 10 per cent of properly managed acute cases. Under other circumstances we have seen the incidence as high as 28 per cent. The ultimate prognosis is unknown.

Undoubtedly a small number of cases develop some type of fibrosis or cirrhosis of the liver but this group is thought to be relatively small.[6, 7] On the other hand, late follow-up studies in "catarrhal jaundice" indicate that a substantial percentage of such cases suffer a permanent lowering of the liver reserve.[8, 9, 10] It is not unlikely, as suggested by Bloomfield,[11] that the milder acute cases, being the ones that receive little or no treatment, are the most likely to develop significant liver damage.

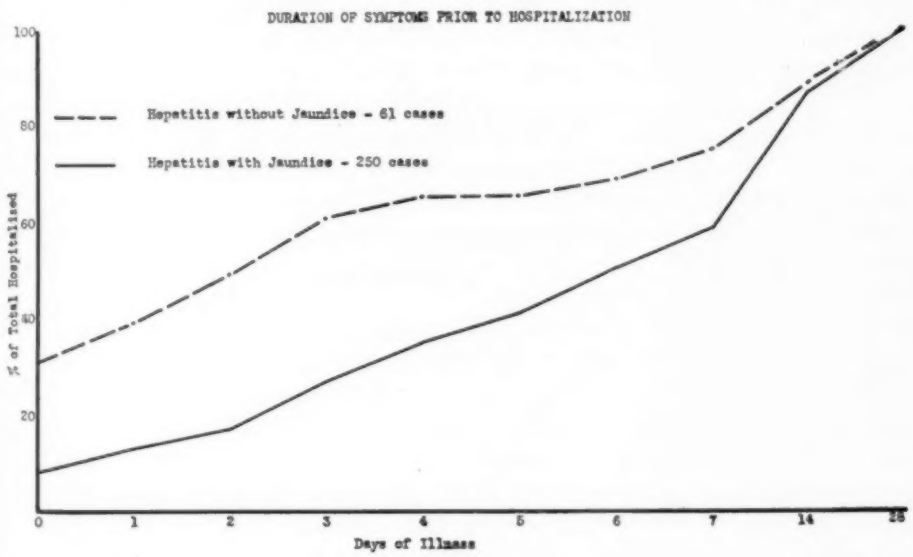
From the above data it must be concluded that infectious hepatitis is a disease of serious potentialities and should be treated accordingly.

THE CARDINAL PRINCIPLES OF TREATMENT

In most cases of acute liver cell injury the diagnosis is made and treatment is begun only after a large proportion of the damage has occurred. Therapeutic efforts must therefore be directed towards the prevention of further damage and towards the aiding of natural reparative processes. Dramatically effective measures are not to be expected. Our experience

indicates that there are only three major therapeutic principles of proved value in infectious hepatitis. These are bed rest, diet and the avoidance of additional factors injurious to the liver.

Bed Rest. Detailed evidence regarding rest and exercise in hepatitis will be presented elsewhere.[12] Suffice it to say that we were the first to demonstrate that in the presence of active hepatitis, exercise will produce an exacerbation of the disease.[2] Thus, failure to go to bed during the acute icteric stage has apparently caused cases of only moderate severity to progress to a fatal outcome over a period of weeks. In other instances the severity and duration have apparently been greatly increased. In the convalescent stage, after jaundice has cleared and the physical findings and symptoms have become minimal, but before sufficient recovery has occurred, exercise may induce a return of jaundice with a severe and prolonged clinical relapse.[2, 12] Finally, cases of acute hepatitis put to bed during the first few days of illness apparently are less likely to develop jaundice than those who remain ambulatory. This is shown in graph 1 where the rate of hospitalization in

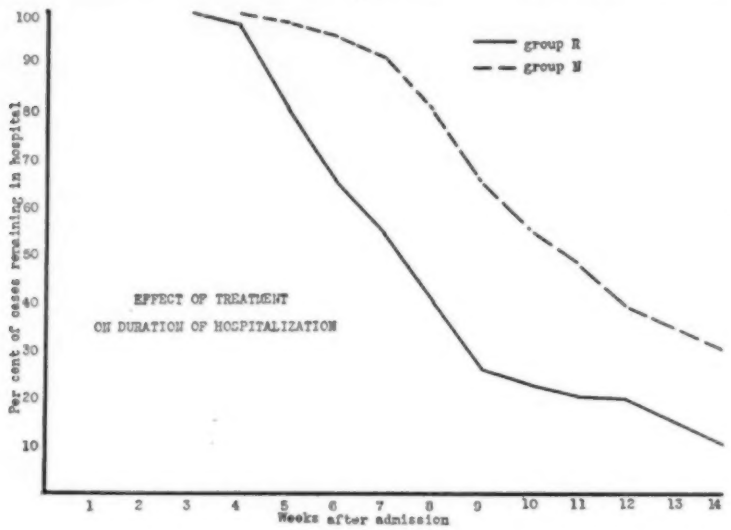


GRAPH 1.

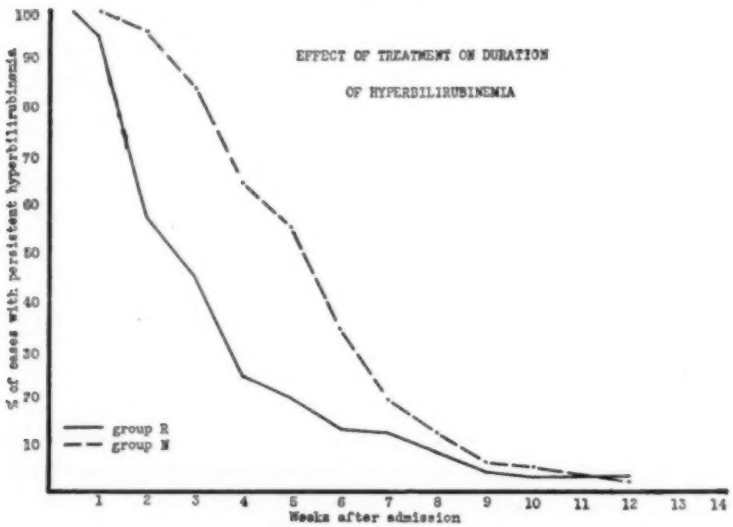
relation to the duration of symptoms has been plotted separately for acute hepatitis with jaundice and acute hepatitis without jaundice. Three hundred eleven consecutive acute cases were included. Since in this instance, jaundice is a sign of comparative severity, it is clear that exercise has a deleterious influence very early in the disease. In fact, there is evidence from infected volunteers [13] that those who exercise shortly after exposure are more likely to develop the disease.

As would be expected from the above data it has repeatedly been observed that patients who remain at strict bed rest for an adequate period of time

recover more promptly and more regularly, while those who have only a short period of bed rest or fail to keep strictly in bed have a longer period of illness and are much more likely to develop the chronic form of the disease. This is demonstrated in graphs 2 and 3. Here are shown the duration of



GRAPH 2.



GRAPH 3.

hospitalization and the duration of hyperbilirubinemia in two carefully studied and comparable series of cases of acute hepatitis with jaundice. Group "N" consisting of 81 cases had poor bed rest whereas group "R" including 74 cases had strict and adequate rest. In addition group "N" re-

ceived the usual average protein, low fat and high carbohydrate diet but group "R" ate a high protein, moderate fat and high carbohydrate diet. It is impossible, of course, to determine the relative rôles of diet and rest in these groups. Although both were probably factors it is felt that rest was the more important. Hughes has made similar observations on smaller groups with essentially the same results.[14] It will be noted that not only was recovery more rapid in group "R" but that the percentage remaining in the hospital at the end of the period of observation, 14 weeks, was much smaller. This last figure includes the so-called chronic cases.

For practical purposes bed rest should be instituted as early in the disease as possible and should be maintained until the criteria to be discussed later are met. It should be as strict as feasible. Bathroom privileges are permissible in all but the seriously ill.

Diet. There is ample experimental evidence that a diet high in protein is most desirable in acute liver injury.[15, 16, 17] We believe, as does Hoagland,[13] that for the present there is insufficient evidence concerning the harmful effects of fat to warrant more than moderate restriction. However, an excess of fat other than butter fat in the diet is poorly tolerated and may result in severe anorexia. Carbohydrates should be high in order to spare protein as well as to provide calories.

It has not been possible to demonstrate the effect of diet as clearly as in the case of rest. The improved results obtained in group "R" over group "N" (graphs 2 and 3) are in all probability due in part to the change in diet. However, the high protein diet was more appetizing so that the total caloric intake was greater. Thus we cannot be certain that the proteins played a dominant rôle although this seems likely on theoretical grounds. In another less carefully controlled investigation involving two groups of cases of about 25 patients each where the only variable factor was the diet there was a significant difference in the duration of the disease in favor of those on the high protein diet. Finally, it was repeatedly observed that patients who were under-nourished at time of onset of the disease were likely to be severe cases and that underweight patients who failed to gain weight usually ran a protracted course. It thus appears that malnutrition which probably involved a deficiency in protein was an important factor influencing the degree and duration of liver injury in many of our cases.

In civilian practice where most patients are well nourished, diet is probably a less important factor. However, it may become of great importance where malnutrition is present or where there is prolonged anorexia and failure to eat. In the latter case it is desirable to provide protein in the form of plasma or amino acids by vein. For the average case a diet of protein 200 grams, fat 65 grams, and carbohydrate 300 grams is recommended. This amount of protein is readily obtained by the liberal use of skimmed milk powder and cottage cheese. Enough fat in the form of butter and cream must be employed to make the diet palatable.

The addition of methionine or choline has not produced clear cut results

either in our experience or in that of others.[13]. This is probably because in man there is rarely a sufficient degree of deficiency in these substances to allow for a demonstrable effect in the small sized groups in which it has been employed. In certain chronic forms of liver disease the situation, however, may be different.

Avoidance of Additional Liver Trauma. The third principle of treatment is the avoidance of additional liver trauma. An already injured liver is extremely sensitive to toxic agents which ordinarily would have little effect. This is especially important during the prodromal and early icteric stages when the maximal degree of acute liver cell damage is present. At this point in the disease additional liver trauma may result in acute liver failure and death. Later in the course, an exacerbation is the usual result.

The most common causes of additional trauma are surgical operations, secondary infections and exposure to various toxic substances, notably alcohol. The first is probably injurious to the liver both because of factors connected with the tissue trauma incident to surgery and because of the anesthetic. Ether, chloroform and possibly ethylene are probably the most dangerous anesthetics. In case of emergency, local or spinal is recommended.

Secondary infections of all varieties have a deleterious effect in infectious hepatitis. This is especially true of malaria, diarrheas and virus pneumonia which by themselves produce marked alterations in liver function indicating liver injury even in the normal liver. As far as possible they must be avoided or promptly controlled. In this connection we have found that the incidence of respiratory infections is about twice as high in hepatitis wards as in other medical wards, indicating a lowering of resistance.

Alcohol is contraindicated in all stages of hepatitis. It has frequently been observed to produce severe exacerbations. Saline purges and other cathartics appear to be harmful, probably because of the associated diarrhea. Enemata should be employed for constipation. Opiates and the short acting barbiturates that are probably detoxified or excreted by the liver have a prolonged and exaggerated effect in the presence of liver disease. We have seen acute fatal morphinism after ½ grain and have seen patients sleep for 36 hours after 3 grains of amytal. Whether these and similar drugs damage the liver is uncertain but they must be used with caution.

To summarize, early and prolonged bed rest, adequate protein intake, and avoidance of additional liver injury throughout the course of the disease are the cardinal principles of treatment. In the interest of clarity the details of management in each stage will be discussed separately.

Prodromal Stage

The chief problem in this stage of the disease is the question of diagnosis.[18] When there is reasonable suspicion of infectious hepatitis it is best to treat the case as such and await developments. Confirmatory findings, especially jaundice, should appear within 10 to 14 days. If at the end of this time the

diagnosis cannot be established the patient should be allowed out of bed and carefully watched for at least a week. The development of a large and tender liver or other evidence of liver pathology as manifested by aggravation of liver function tests indicates the presence of hepatitis and the patient must be immediately returned to bed.

Treatment in this period is symptomatic except for rest and diet. Particular care must be used to avoid additional liver injury. This point requires emphasis because patients in this stage of the disease are potentially much more seriously ill than they appear. Relatively minor operations especially under ether may precipitate liver failure and death. Occasionally these are performed for some unrelated condition on the assumption that the patient has recovered from a mild acute respiratory or gastrointestinal infection. In other instances hepatitis may produce a picture simulating acute appendicitis, cholecystitis or ruptured peptic ulcer. It is well to remember that acute abdominal pain and rigidity occur only, in our experience, in the presence of an enlarged and tender liver.

Acute Icteric Stage

The appearance of jaundice usually settles the diagnosis. Since it is impossible to predict the degree of severity for a few days to a week or more after the appearance of icterus or until the bilirubinemia has reached its peak and has commenced to fall, it is best to treat all cases as potentially severe until proved otherwise. Strict bed rest must be enforced. A high protein intake should be maintained, if necessary by the use of intravenous amino acids or plasma. This is especially desirable where nausea and vomiting last for more than a few days. Glucose can be given in a similar fashion.

In our experience the acute symptoms associated with the appearance of jaundice are best controlled by maintaining a fluid intake of at least 3000 c.c. daily. Chilled skimmed milk is especially desirable because it supplies both protein and fluid and is well tolerated. If fluids are given intravenously it is important to avoid normal saline since marked aggravation of the size and tenderness of the liver and even generalized edema is readily produced. As is well known there is a definite tendency towards fluid retention in this disease and we have often noted increase in the liver size when fluids are pushed by mouth. Thus, it is best to employ 5 or 10 per cent glucose in water for intravenous use except where vomiting is severe when salt may be used with caution. Forcing of fluids usually results in prompt abatement of symptoms within a few days.

Although the immediate prognosis is difficult to determine at the beginning of jaundice, a history of previous liver injury, age over 40 years, poor nutritional condition and the presence of complicating infections are suggestive findings. A bilirubinemia that rises rapidly for four or five days to high levels especially in the absence of a prodromal period and a persistently high bilirubinemia for a week or more associated with persistent nausea and vomiting are also suggestive signs. We have been able to show

a definite correlation in several large series of cases between the maximum icterus index and the severity and duration of the disease. Thus when the icterus index rises to 100 or more, recovery will require over three months in 50 per cent of cases.

In the more serious cases vitamin K should be given if the prothrombin time is elevated or if bleeding is noted. The dose should not be over 5 mg. parenterally as Shapiro [19] has shown that larger amounts may depress liver function. If the prothrombin time continues high, transfusions are indicated. Hypoglycemia must be watched for and treated by the frequent or constant administration of glucose. Occasionally ascites is seen in severe acute cases. This rarely requires special treatment except for care in the administration of salt and fluids. It does not indicate that cirrhosis is present since it spontaneously disappears as recovery progresses.

Certain additional points regarding therapy should be mentioned. Cathartics and especially salts are contraindicated. Bile salts are without benefit and may be harmful. Atropine is to be preferred to opiates for cramps which are sometimes troublesome. In severely ill cases salicylates may further increase the prothrombin time to dangerous levels.[20] There is evidence that thiamine chloride in large doses may be toxic to the liver,[15] so it is best to use only small doses parenterally if at all. Since it has been found that the sulfa drugs may be toxic to the liver at least in certain individuals,[21, 22] penicillin is to be preferred for complicating infections requiring specific therapy.

Acute Hepatitis Without Jaundice

This mild form of acute infectious hepatitis runs a shorter course than the more severe icteric type. However, the principles governing management are identical. If treatment is not strictly enforced, which is often difficult, the course is unnecessarily prolonged and sequelae may occur.

Convalescent Stage

The importance of maintaining the hepatitis patient on bed rest until recovery is sufficiently advanced has already been discussed. The practical question is how to determine when this point has been reached. Obviously, if a patient with certain abnormal findings while at bed rest is allowed to return to work after an appropriate interval on an ambulatory status and then develops an exacerbation or relapse of his hepatitis, his original findings can be said to have indicated persistent activity of his liver disease. In order to insure controlled conditions a graduated exercise tolerance test was substituted for the return to work and a careful study made of the relation of initial findings to the outcome of the test.[2, 12] The first series of patients, consisting of 184 consecutive cases of infectious hepatitis, were tested when they had reached a stage of recovery considered satisfactory by the local ward physician on the basis of pre-war criteria.

TABLE II

Significance of Various Findings Prior to Exercise in Relation to Outcome of Exercise Tolerance Test

Finding	Number of Cases	% Pos. Exer. Tol.
1. Liver normal size	106	31
Liver borderline size	38	45
Liver enlarged (non tender)	40	75
2. Normal bromsulfalein (5 mg./kg.)	32	34
3–4% retention in 1 hr.	21	43
5–9% retention in 1 hr.	31	48
10% plus retention in 1 hr.	11	91
3. Negative Hanger test	115	38
1+ or 2+ positive (24 hrs.)	12	50
3+ or 4+ positive (24 hrs.)	24	62
4. Normal alkaline phosphatase	69	48
4.0 or more Bodansky units	20	75
5. Normal sedimentation rate	86	45
Elevated sedimentation rate	30	53

An analysis of these results is presented in table 2. Forty-three per cent of the 184 cases had an abnormal test, equivalent to an exacerbation of the hepatitis, demonstrating the inadequacy of our original criteria for recovery. It will be noted that marked elevation of the bromsulfalein and enlargement of the liver are the most significant findings whereas elevation of the sedimentation rate is of little value. Also, active hepatitis may be present even though the liver and the bromsulfalein retention are normal prior to exercise. This is only partly explained by many patients having more than one positive finding. The value of further intercorrelations is limited by the numbers involved but it appears that liver enlargement or abnormal bromsulfalein retention alone is frequently significant whereas an abnormal phosphatase level or cephalin cholesterol flocculation alone is usually not.

Serum bilirubinemia is not included in the above table because of the inaccuracy of icterus index determinations at low levels. Unfortunately it was impossible to use an accurate method routinely in this particular group. Patients with clinical jaundice were never deliberately exercised. Subsequent observations, however, show that an icterus index over 20 units or a prompt direct Van den Bergh reaction is practically always associated with active hepatitis. On the other hand an elevated indirect type of Van den Bergh can only be classified as suggestive of activity. In addition to the above findings the persistence of symptoms, the presence of complicating infections, a history of previous liver damage or if the preceding acute attack was severe or in a person over 40 years of age increase the probability of persistent activity of the hepatitis.

As a result of this study the following criteria were formulated to be met before the termination of bed rest. They are applicable equally to acute hepatitis with and without jaundice.

Criteria for Ambulatory Status. (1) At least three weeks' bed rest. (2) Liver—not enlarged and not tender. (3) Absence of symptoms especially lassitude, diarrhea, intestinal cramps, flatus, headache and anorexia.

(4) Normal serum bilirubin for one week. If slightly elevated, the direct Van den Bergh must be negative. (5) Bromsulfalein under 10 per cent in one hour (5 mg./kg.—dose) and preferably under 5 per cent.

Also, if available, the cephalin cholesterol flocculation test should be 2 + or less in 24 hours and the alkaline serum phosphatase under 4.0 Bodansky units. If only one finding is positive keep patient in bed one extra week and then try on ambulatory status.

Even when the above criteria are met, some 10 per cent of patients will still show an abnormal exercise tolerance test. Consequently, it is felt that these criteria are not too drastic for civilian practice. It can be argued that since civilian patients may be returning to sedentary jobs their recovery need not be as complete as in the army. To some extent this is true and we are well aware that there are patients who can return to work after only a week in bed, but it is impossible to select these cases beforehand. Recent experience with civilians has confirmed our observations in the army.

In civilian practice an exercise tolerance test is not necessary or feasible as an index of recovery, but, as a substitute, patients should be followed carefully for several weeks after returning to work to insure proper convalescence and determine if they have really recovered. If a significant degree of active hepatitis is still present as indicated by the development of an enlarged tender liver or a sharp increase in the bromsulfalein retention the case should be returned to bed at once. If this is not done disability will persist for several months at least and not infrequently we believe that chronic hepatitis will develop.

Chronic Hepatitis

The management of this stage of infectious hepatitis has been previously discussed in some detail.[3] Due to the very slow rate of recovery it is necessary to be more conservative in the interpretation of the "criteria of recovery" than in the acute disease. Table 3 shows that other findings being equal a case of chronic hepatitis is almost twice as likely to have an abnormal exercise tolerance as an acute case.

Table III

Relation of Type of Hepatitis to Outcome of Exercise Tolerance Test

Finding	Number of Cases	% Pos. Exer. Tol.
1. Acute hepatitis	130	36
Chronic (3 mo. plus) hepatitis	54	61
2. Liver normal or borderline in size in acute hepatitis	103	28
Liver normal or borderline in size in chronic hepatitis	41	51

It is important to eliminate all complicating infections. Dental and other foci, amebiasis and malaria should always be ruled out. Non-specific diarrhea, if present must be controlled even if it appears to be the result of the hepatitis. Often this can be accomplished with vioform, sulfaguanidine or dilute hydrochloric acid by mouth. Sometimes crude liver extract intra-

muscularly is effective suggesting that the diarrhea is related to some form of nontropical sprue.

Good nutrition must be maintained. Patients that are underweight and fail to gain rarely do well. The regular hepatitis diet should be used but with particular emphasis on the total caloric intake. Hoagland [18] has suggested intravenous liver extract. In our experience this treatment is difficult to evaluate but it apparently is of benefit in some cases. The same can be said of choline and methionine.

Patients with so-called inactive hepatitis,[3] that is with evidence of liver damage but with a normal reaction to exercise, do not require bed rest. It is, however, desirable for them to follow the dietary treatment.

Discussion

It is of interest to speculate as to why infectious hepatitis appears to be more severe at present than formerly. If is, of course, quite possible that we are now dealing with a different virus or perhaps a more virulent strain. The age factor is of some importance since our cases have been entirely adults where the disease is probably more severe than in children. On the other hand, obvious signs even of severe liver disease are few and the clinical picture of chronic hepatitis has until recently been obscure.[3] Perhaps sequelae occurred but were unrecognized or misdiagnosed. In this connection it should be mentioned that extensive experience during the last year in this country both in the army and among civilians has revealed no essential differences in the disease from that which we studied in Africa, Italy, France and the Near East during the war.

Perhaps the most important result of the study lies in the application of findings made in infectious hepatitis to other etiologic types of acute liver disease. Infectious mononucleosis, virus pneumonia, acute brucellosis and probably many other infections are frequently associated with liver injury. It is not unlikely that residual symptoms are often due to a residual hepatitis, much of which might be averted by paying more attention to the liver and by applying the principles of management that we have learned from infectious hepatitis.

Summary

1. Evidence is presented to show that infectious hepatitis is a more serious disease than was previously thought and that it therefore should be treated accordingly.

2. The cardinal principles of treatment are early, strict and sufficient bed rest, high protein, moderate fat and high carbohydrate diet and avoidance of additional liver trauma. Evidence is presented to show that these measures are effective in reducing the duration of the disease and the incidence of relapse and chronicity.

3. Details of management in the different stages of the disease are discussed.

4. The problem of determining when recovery has become sufficiently advanced to allow the patient out of bed has been investigated by means of an exercise tolerance test. This has resulted in the formulation of a set of criteria which differ materially from pre-war ideas. Their use results in 90 to 95 per cent of cases making a prompt and satisfactory clinical recovery.

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REFLEX SYMPATHETIC DYSTROPHY; REPORT ON 57 CASES *

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Reflex sympathetic dystrophy is usually referred to as causalgia because of its chief symptom—an agonizing burning pain. The former term is preferable, however, because in many patients with reflex sympathetic dystrophy the distinguishing features are not pain but other manifestations of sympathetic stimulation, namely, rubor, pallor, or both, swelling, sweating and often mottled or cystic atrophy of the bone. Atrophic changes in the skin and muscles may be prominent. The characteristic feature of sympathetic pain is its deep, burning nature, felt diffusely through the part affected, often occurring in acute exacerbations on use of the limb or on pressure over trigger points. A less frequent painful feature may be muscle cramp. A background of vasomotor instability is very common, together with a hyperemotional temperament or even hysterical stigmata that frequently lead to a mistaken diagnosis of psychoneurosis. This fact has often led to many injustices to the patient, both personally and in the settlement of industrial cases.

A case in point concerns a patient who sprained her arm lifting heavy drums over her head. Thrombophlebitis of the brachial and subclavian veins followed. For a year she suffered severe pain in the upper arm, became highly hysterical and emotional and was turned down before the industrial commission for proper compensation. When she was first examined, rubor of the lower arm and hand was present, together with swelling and increased sweating. Two cervical sympathetic metycaine blocks gave her 90 per cent relief of pain, together with disappearance of definite trigger points. For some reason unknown to me I never could persuade her lawyer to reopen her case.

Mitchell, Morehouse and Keen wrote the first brilliant description of this distressing phenomenon, based on cases of gunshot wounds to nerves and blood vessels in the Civil War. Sudeck described cases of painful joint involvement, giving rise to the term Sudeck's syndrome. Leriche pointed out most vividly the rôle of the sympathetic system in this pernicious reflex, and Homans, in his presidential address to the Massachusetts Medical Society in 1940, described the clinical features and the successful treatment of several cases of "minor causalgia." To Livingston, in his scholarly monograph on "Pain Mechanisms" credit should be given for the clearest theoretical elucidation of the reflex itself. I have borrowed heavily from his theory to explain the vicious circle producing the syndrome of reflex sympathetic dystrophy in the diagrams and ideas expressed in this article.

* Read at the Twenty-seventh Annual Session of the American College of Physicians, Philadelphia, May 15, 1946.

De Takats has recently reviewed 54 cases of causalgic states, in which he recognizes three sensory levels, peripheral, spinal and cortical, based on lesions of the first, second and third neurons. He advocates direct treatment to the affected neuron. With few exceptions our therapeutic attack has been on the second neuron, namely the sympathetic pathway, either by sympathetic metycaine block or by sympathectomy. It is our conviction that the majority of these patients can be relieved by these two therapeutic methods. In severe causalgic states treatment of the trigger points alone is not very satisfactory in our experience, and has been used chiefly as an adjunct to metycaine block and sympathectomy.

Mechanism of Reflex Sympathetic Dystrophy

Figure 1 illustrates diagrammatically the nervous pathways giving rise to the syndrome of reflex sympathetic dystrophy. The fundamental concept of the internuncial pool (figure 2), a theory advanced by Lorente de No and adopted by Livingston, can be explained simply as follows. A prolonged bombardment of pain impulses sets up a vicious circle of reflexes spreading through a pool of many neuron connections upward, downward and even across the spinal cord, and perhaps reaching as high as the thalamus itself. In accordance with the principle of "summation of nervous impulses," and with the theory of "facilitation" of conductivity within the spinal cord as described by Porter and Taylor, there is kept alive within such a pool a constant circling of activity across the synapses involved. Some of these synapses include the sympathetic motor neuron cells in the lateral horn, controlling vasomotor tone and the sweat glands. Spasm in the arteriolar and the venule ends of the capillary loops raises filtration pressure, and edema and swelling result. Cyanosis and anoxemia increase capillary permeability and filtration, further augmenting edema. Other synapses involved may be the anterior motor horn cells, giving rise to skeletal muscle cramps and spasms. Augmented stimuli to pain also flow out of the pool, traveling up the thalamic tract. Depending on the extent of the pool, we detect the phenomena of pain and sympathetic disturbances observed a long distance from the injured area of the body and occasionally even spread to the contralateral side.

Etiology

The source (table 1) of the reflex sympathetic dystrophy syndrome was traumatic in 31 of our 57 cases; secondary to operative procedures in six; to static defects of the foot in four; to thrombophlebitis in five; and to a scalenus syndrome accompanied by a Raynaud's syndrome in two. The traumatic cases were divided as follows: fractures 12; sprains 12; bruises 5; lacerations, occupational trauma and bismuth injection outside of vein in one each. Under operative procedures, there were four amputations; one mangled hand and amputation of a finger; and one ligation of a varicose

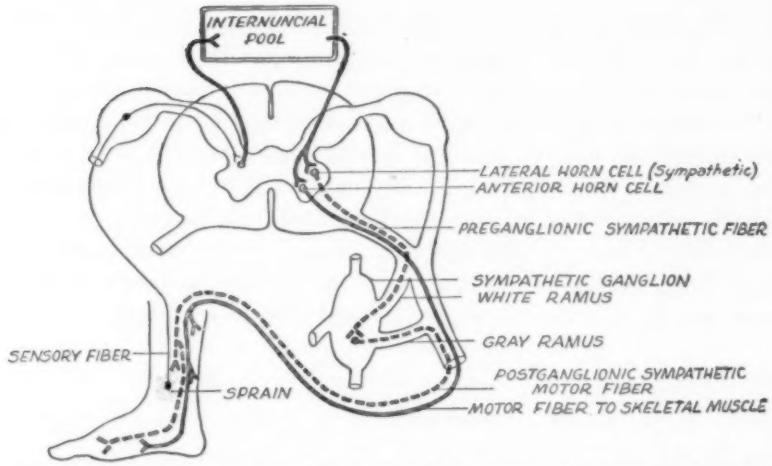

FIG. 1. Diagram of nervous pathway of reflex sympathetic dystrophy. The afferent pathway is represented on the reader's left, the efferent on the right. Below the anterior horn, the open line represents the sympathetic fibers, the heavy solid line the motor nerves. (From Surg., Gynec. and Obst., Jan., 1946.)

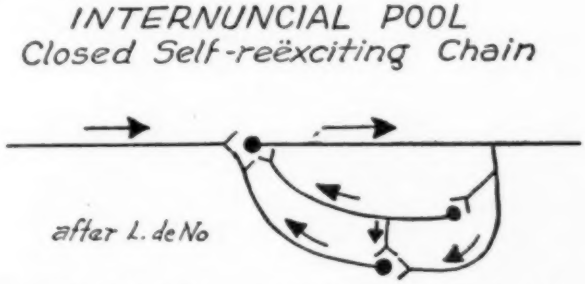

FIG. 2. Diagram of de No's theory of the internuncial pool. (Adapted from Jr. Neurophysiol., 1938, i, 207.)

TABLE I

Etiology in 57 Cases

Traumatic		31
Fracture	12	
Sprain	12	
Bruise	5	
Laceration	1	
Occupational	1	
Bismuth injection outside vein	1	
Operative procedures		6
Amputation	4	
Mangled hand and amputation	1	
Ligation varicose vein, ulcer at site	1	
Static defect of foot		4
Thrombophlebitis		5
Spontaneous hematoma involving peroneal nerve		1
Malum coxae senilis, nailing of hip		1
Osteomyelitis		1
Thalamic syndrome, cerebral hemorrhage		1
Plantar wart		1
Gonorrheal arthritis		1
Scalenus syndrome with Raynaud's syndrome		2
Anterior poliomyelitis		1
Subacromial bursitis		1
Intervertebral disk herniation		1

vein, resulting in a chronic ulcer at the site of operation. There were single cases with the following diagnoses: spontaneous hematoma, involving the peroneal nerve in a patient with hypoprothrombinemia resulting from nontropical sprue; malum coxae senilis and nailing of the hip; osteomyelitis; thalamic syndrome due to cerebral hemorrhage; plantar wart; gonorrheal arthritis; anterior poliomyelitis of 25 years' duration; subacromial bursitis complicated by angina of effort; intervertebral disk herniation.

Exacerbating factors were operative procedures in seven cases, fungus infection in three, pes planus in two, thrombophlebitis in two and, in one case each, osteomyelitis, scalenus syndrome and angina of effort.

Pain

Pain is almost always present and may be so severe and so long persistent that the patient contemplates suicide. Causalgic pain mediated by the sympathetic system has characteristic features of its own. It is a deep, boring "toothache-like" pain, diffuse in its distribution, difficult for the patient to localize, not felt precisely in the area of the old injury. Manipulation, as in physiotherapy, and use of the limb involved, aggravate the suffering. As stated previously, the pain is often described as "burning." One or more trigger areas are present. These trigger zones may be widely separated and some of them far from the site of original injury. A chief trigger zone is usually found near the original injury, however, and blocking this area with procaine may cause the other trigger points to disappear. Thus, blocking a trigger point is an additional diagnostic and therapeutic method of attack. Pressure on a trigger point characteristically causes a diffuse spread of the pain over a wide area, usually cephalad.

Table II

Pain

Severe or causalgic	34
Moderate	21
None	2
Trigger points	36

In our 57 cases (table 2), trigger points, single or multiple were found in thirty-six. Pain was severe or causalgic in 34, moderate in 21 and absent in two. These last two patients showed other signs of reflex sympathetic dystrophy.

Other Symptoms and Signs (Table 3)

Rubor was a more frequent finding than pallor in our patients, although they more often complained of a cold than of a hot limb. Rubor was present in 30, pallor recorded in 13, and swelling in thirty. Increased sweating is a very important indication of sympathetic stimulation and should always be carefully sought for, both by questioning and by observa-

TABLE III

Other Symptoms and Signs

Rubor	30
Pallor	13
Swelling	30
Sweat	29
Atrophy	
Skin	8
Muscle	14
Bone	
Mottled or cystic	9
Diffuse (disuse)	9
Cramp	4

tion. This feature was present in 29 of our patients. Atrophy of the skin was seen in eight and atrophy of the muscle in 14 cases. The typical bone atrophy of reflex sympathetic dystrophy has a mottled or cystic appearance in roentgen films (figure 3). The atrophic changes are probably due to spasm of the nutrient arteries. The findings are typical of the so-called Sudeck's arthritis. Such changes were noted in the roentgenograms of nine patients. A diffuse atrophy of disuse was seen in another nine cases. Four patients had muscle cramps, this feature being more often seen in those who have had old deep thrombophlebitis.

FIG. 3. Mottled bone atrophy of Sudeck's arthritis. Sprain of left foot five months before. Improvement spontaneously three months after this roentgenogram was taken. Right foot shown for contrast.

Diagnosis

Either cervical or paralumbar sympathetic procaine block will serve as a diagnostic therapeutic test. The relief of pain may be almost miraculous but even if not so dramatic will serve to establish the diagnosis, provided disappearance of other phenomena is also noted, such as relief of sweating, increased warmth and comfort in a cold member associated with rise of skin temperature (temperature index test); and disappearance of trigger points (figure 4).

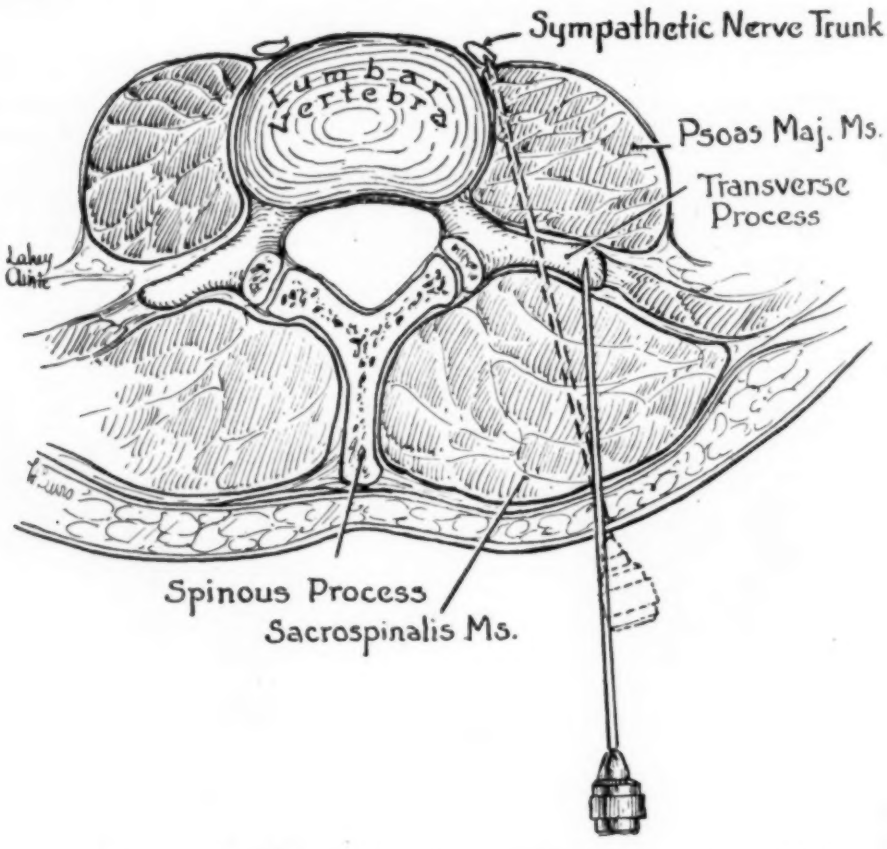

Fig. 4. Technic of paralumbar metycaine sympathetic block. (From Nicholson, Anesth. and Analg., May–June, 1942.)

Treatment

The ideal point of attack would be the internuncial pool itself. So far, no direct effective means is at hand to stop the vicious circle within this pool of neuron synapses.

Two other points of attack exist: the trigger points and the sympathetic pathway. Repeated injections of the trigger points usually are necessary.

If the sympathetic pathway is blocked by procaine, one is occasionally gratified by the astounding relief obtained with only one injection. More often, there are relapses within a few days or weeks and repeated injections are necessary at longer and longer intervals. It would seem more logical to give a series of three injections, one every second day, for the permanent rupture of the pernicious reflex, a method so successfully applied to thrombophlebitis.

At the Lahey Clinic we have felt it best to resort to sympathectomy in the majority of our treated cases, after the demonstration of the efficacy of one block, in order to obtain the maximum of relief and the greatest assurance of permanency of relief.

Posterior root rhizotomy, cordotomy or, for pain from a high cervical segment, interruption of the thalamic pathways in the medulla and even resection of the sensory cortex may be necessary in exceptional cases. In none of our cases have we resorted as yet to these more radical measures, although in one unsuccessful result after sympathectomy, we are considering interruption of the thalamic tract. This was the case of a woman who had suffered a laceration of the hand, and two repair operations one year before. She had severe causalgic pain. Trigger points, pallor, sweating, muscle and bone atrophy were present. Sympathetic block gave no relief and a year after sympathectomy there was no relief. She is to have resection of the operative scar on the wrist with a pedicle skin graft done before interruption of the thalamic tract will be carried out.

TABLE IV

Results of Block on Pain in 36 Patients

Block as only therapy	12
100% Relief for 1 month or more	4
100% Relief—follow-up less than 1 month	5
90% Relief for 1 month or more	1
50–90% Relief—follow-up less than 1 month	1
Temporary relief—sympathectomy refused	1
Block with temporary relief and sympathectomy done later	24

Twenty-four patients (table 4) received sympathetic procaine block, with varying amounts of relief of pain and sympathetic phenomena in all but two. Twelve patients were treated by block alone. Of these, four obtained complete relief for one month or over and five who were followed less than one month received at least temporary complete relief. One patient had 50 to 90 per cent relief for one month or over, and another patient the same amount of relief, though she has had a follow-up of less than one month. One patient received temporary relief after metycaine block as the only method of therapy and refused sympathectomy. Another patient who had injection of trigger points as well as sympathetic procaine block obtained relief for only three weeks and sympathectomy was performed later.

TABLE V

Results of Sympathectomy on Pain in 29 Patients

100% Relief 1 month to 2 years	10
100% Relief—follow-up less than 1 month	1
50–90% Relief 1 month to 2¼ years	11
0–25% Relief more than 1 month	7

Twenty-nine patients have undergone sympathectomy (table 5). Ten obtained complete relief for follow-up period of from one month to two years. One patient received complete relief but was followed for less than one month. Eleven patients had 50 to 90 per cent relief for periods ranging from one month to two and a fourth years. Seven patients received little or no relief and were followed over one month.

An analysis of the seven poor results from sympathectomy is shown in table 6. Five obtained no relief whatsoever. In two of these, diagnostic

TABLE VI

Analysis of Poor Results from Sympathectomy

No relief	5
Diagnostic block gave no relief (casts doubt on diagnosis)	2
Diagnostic block not done first	1
Scalenectomy needed	1
Angina of effort returned	1
25% relief only	2
Exploration of radial nerve advised	1
Continued physiotherapy for pronated feet, advised	1

blocks had given no relief either. One of these two patients has been discussed. The second patient who received no relief from either block or sympathectomy had sustained a fractured right ankle three years before. Her pain was severe, of the causalgic type; trigger points, rubor and swelling were present. For three months following sympathectomy she was considerably better and was able to abandon crutches. At a nine month follow-up examination, however, her pain was as severe as ever, although a good sympathectomy effect was evident and swelling was no longer present. This patient is to be tested by a peripheral peroneal and sural nerve block. The electrical resistance of the skin is to be studied for evidence of regeneration of the sympathetic nerves. She also needs operative correction of the foot, but our experience with such operations has been disappointing unless the causalgic state has first been cured.

Our experience with these two patients will make us hesitate in the future to offer sympathectomy to patients who received no relief following sympathetic block.

The third patient who had no relief following sympathectomy had his operation done elsewhere, without diagnostic block as advised by us, being carried out first. A fourth patient we feel needs a scalenectomy for further relief. The fifth patient who received absolutely no relief from sympathectomy suffered a peculiar pain in the left arm, axilla and chest, often

provoked by effort but more often coming on while lying down. Successful treatment of a left subacromial bursitis gave him no permanent relief. Three paravertebral sympathetic metycaine blocks and two trigger blocks gave him complete but temporary relief. An upper thoracic, left sympathectomy afforded him relief for only two or three weeks, and two months later he reported full return of angina of effort.

In two patients who received only about 25 per cent relief following sympathectomy, an additional exploration of the radial nerve is advised for one patient and the other needs continued physiotherapy for pronated feet.

Most unfortunately, a cervical sympathetic block in one patient resulted in an injury to the spinal cord, giving rise to a Brown-Sequard syndrome, leading to disability and pain in the left arm and right leg. He has, however, been free from his old causalgic pain for a year. Another patient has developed a Raynaud's syndrome one year after relief by block alone of causalgic pain resulting from thrombophlebitis. Spontaneous improvement without therapy was noted in two patients.

Summary

Reflex sympathetic dystrophy is described as a syndrome produced often by minor trauma to a limb or local disease, leading to the reflex production of the sympathetic phenomena of rubor or pallor, heat or cold, increased sweating, edema, and pain. Since the factor of pain may be absent, the term reflex sympathetic dystrophy is preferred to causalgia.

The rôle of Lorente de No's "internuncial pool" in the production of the syndrome of reflex sympathetic dystrophy is presented.

Traumatic injury accounted for only 54.4 per cent of the 57 cases reported.

The typical bone atrophy of reflex sympathetic dystrophy is mottled or cystic (Sudeck's syndrome).

Diagnosis depends largely on the demonstration of relief by sympathetic procaine block. Twenty-four of the 57 patients received sympathetic block with procaine, with varying amounts of relief of pain and sympathetic phenomena in all but two patients.

Treatment may be directed to blocking trigger points if they exist and to blocking the sympathetic pathway. In 12 patients treated by sympathetic procaine block alone, four had relief for one month to permanent, five who were followed less than one month had complete relief, one had 90 per cent relief for one month or over, one who was followed less than a month had 50 to 90 per cent relief, and the twelfth patient had temporary relief but refused sympathectomy.

Twenty-nine patients of the 57 here reported had sympathectomy performed, with complete relief of pain in 10 for one month to two years. One patient who had a follow-up less than one month had complete relief. Eleven patients had 50 to 90 per cent relief for periods ranging from one month to two and a fourth years. Seven patients had no, or but little, relief of pain.

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SPONDYLOSIS AND SPONDYLARTHRITIS *

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The spine is a weight bearing structure and an instrument of motion. It resembles in this respect the joints of the lower extremities which likewise serve to bear weight and to carry out certain motions. There is, however, an important difference between the two. In the joints of the lower extremities the weight bearing surfaces are also the gliding surfaces for motion. In the spine the structures concerned with weight bearing are the intervertebral discs and the vertebral bodies while the motions are carried out in joints serving this purpose only. This necessitates a separate discussion of the disorders of the two functions.

I. Disorders of the Weight Bearing Function of the Spine (Spondylosis)

The intervertebral disc undergoes definite changes in the course of life. The nuclear substance normally soft, like jelly, becomes gradually firm and dry due to a process of dehydration. Coincidentally the elastic elements of the disc are replaced with fibrous tissue just as is the case in the skin, lungs and arteries in the course of the aging process. As a consequence, there is a loss of elasticity so that the pressure of the trunk, amounting to a few hundred pounds when a weight is lifted, cannot be counterbalanced. Eventually, according to the experiments of Keyes and Comperes "minute ruptures of the cartilage plate" occur. This chain of events is called degeneration of the intervertebral disc. This process is regularly well distinguishable microscopically. In a certain percentage of cases, about 20 per cent in our experience, as an outcome of the process of degeneration, a thinning of the intervertebral disc results causing a narrowing of the intervertebral space which can be recognized radiographically (figure 4). In the final analysis this is due to the fact that the cartilage has no power of regeneration. Another reaction occurs instead. Just as the fracture of a bone stimulates the periosteum to develop a callus, so do the ruptures of the cartilage plates stimulate the adjacent vertebral bodies to produce new periosteal bone. The newly produced bone has the appearance of a marginal spur (exostosis, exophyt, lipping). The spurs are in the beginning only slightly pronounced, in later stages they are long, broad and variously curved. Large spurs of two adjacent vertebrae may join to form an osseous bridge spanning the intervertebral space. The spurs develop on the anterior surface and the lateral surfaces, occasionally also on the posterior surface (figures 1, 4, 5, 6, 10, 11).

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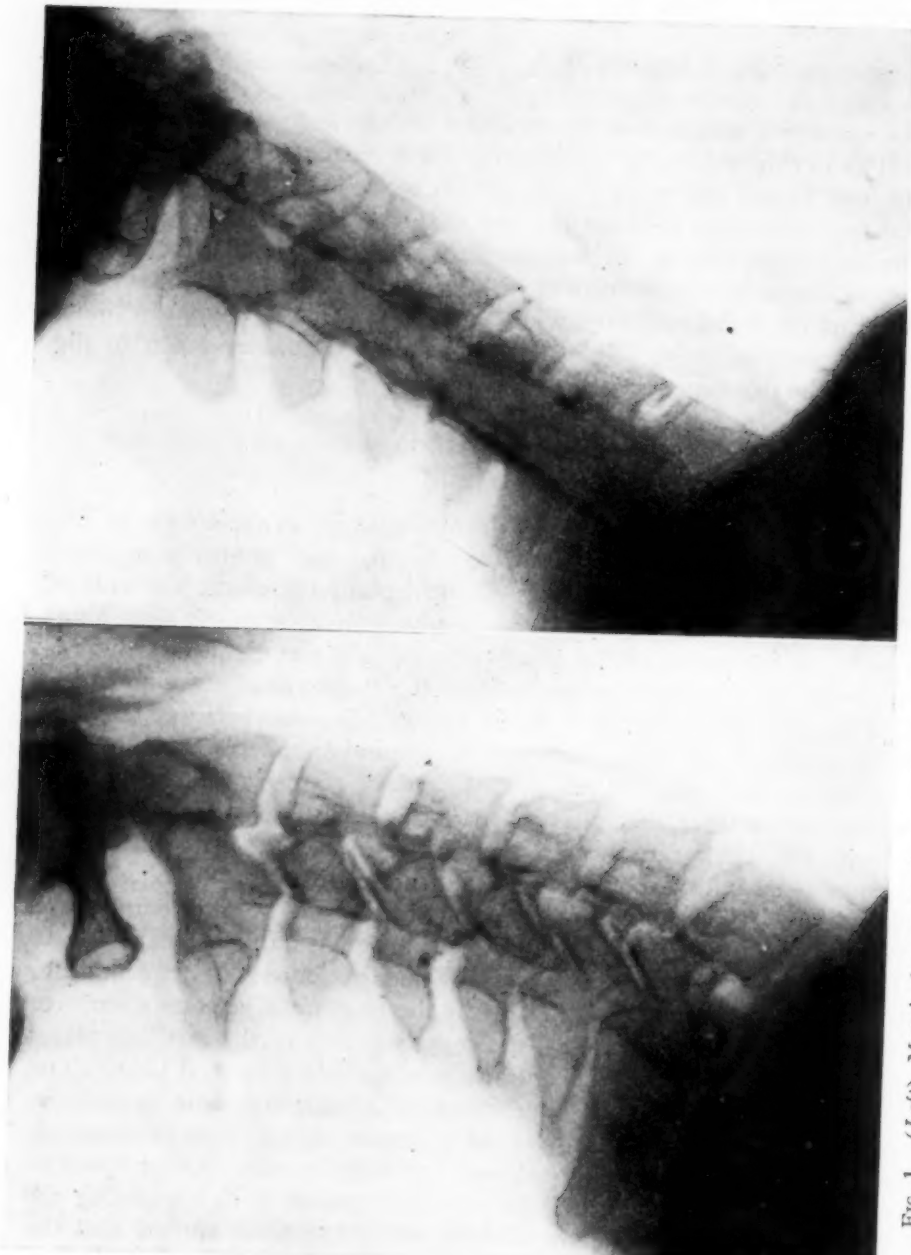

FIG. 1. (*Left*) Marginal spur on the anterior surface of the sixth cervical vertebra causing dysphagia due to its proximity to the esophagus. The apophyseal joints appear normal. Summary: spondylosis, no spondylarthritis.

FIG. 2. (*Right*) Osseous ankylosis of all apophyseal joints of the cervical spine. Summary: spondylarthritis, rheu-

In the first year the rapidity of the growth of a spur varies considerably from individual to individual and from vertebra to vertebra. A normal appearing vertebra may develop a spur up to 1 cm. long within the first year. After the first year the growth continues at a very slow rate. Rádiographic examinations usually reveal perceptible changes in the size of the spurs only at intervals exceeding two years.

The two most important factors controlling the growth of the spinal spurs are the body weight and the age.

The heavier the body weight, the earlier in life do the spurs become manifest. Willis found on cadavers that at the age of 45 only 10 per cent of the slender type but 83 per cent of the heavy showed hypertrophic spinal changes, most frequently in the lumbar spine. Furthermore, while at the age of 50 all cases of the heavy type showed marginal spurs, this condition resulted in the slender type at the age of 60 years.

As to the age factor, Feistmann-Lutterbeck found on roentgen-ray films of 1,250 persons the distribution of the marginal spurs as follows:

1% in persons between 20 to 29 years of age
6% in persons between 30 to 39 years of age
48% in persons between 40 to 49 years of age
75% in persons between 50 to 59 years of age
92% in persons between 60 to 69 years of age
100% in persons over 70 years of age

Summarizing, it appears that the marginal spurs are to be considered a reparatory reaction of the vertebral bodies to the degeneration of the intervertebral discs, progressing strictly in proportion to the age of the individual and hastened by the body type. In other words, as an answer to the flattening of the intervertebral disc, that is a diminution in the vertical direction, the marginal spurs tend—as Buckley put it—"to provide a wider articular surface" in the transverse and sagittal direction, and thus to restore the weight bearing capacity of the spinal column.

As to the clinical significance of the spinal spurs, there is a widespread inclination to hold them responsible for numerous clinical symptoms. Backache, stiffness, pain radiating from the trunk to the extremities, limitation of motion of the vertebral column are frequently considered the result of the lipping of the vertebral bodies. It is natural that we welcome the readily demonstrable, optically very impressive radiological findings in the vertebral bodies because they seem to give us a plausible cause for many complaints which otherwise would remain obscure.

Unfortunately, it is often very difficult to explain the causal connection between the changes seen on the roentgenograms of the spine and the clinical findings. The only instances in our experience, in which a marginal spur as such gave rise to clinical symptoms were cases in which large spurs located on the anterior surface of the cervical spine caused symptoms of dysphagia due to their close vicinity to the esophagus (figure 1). In an-

Fig. 1. (*Left*) Marginal spur on the anterior surface of the sixth cervical vertebra causing dysphagia due to its proximity to the esophagus. The apophyseal joints appear normal. Summary: spondylosis, no spondylarthritis.
Fig. 2. (*Right*) Osseous ankylosis of all apophyseal joints of the cervical spine. Summary: spondylarthritis, rheu-

FIG. 3. Narrowing of the apophyseal joint between the fourth and fifth cervical vertebrae with subchondral osteosclerosis. Summary: spondylarthritis, osteoarthritic type, no spondylosis.

other group of cases reported in the literature, spurs growing into the spinal canal gave rise to neurological symptoms. Cases of this kind are exceptional. As a rule, the marginal spurs are not pathogenic. This is so in the first place because of the location of the spurs. How for instance can a spur on the anterior surface of a vertebra produce pain in an arm or leg since no peripheral nerves run in the front of the spine? Spurs are often seen on both sides of the spine while pain is felt on one side only. In other cases, pain is felt on one side while the spurs are present on the other.

There is, apart from the location of the spurs, another reason to doubt the causal connection between the radiological findings and the clinical symptoms. Were the symptoms the result of the spurs, they could never subside and would last permanently, unless the exostosis were removed surgically as is being done in the case of an exostosis of any other localization giving rise to clinical symptoms. Instead, we see that the symptoms for which the spurs are held responsible usually subside following physiotherapy or conservative orthopedic measures while the spurs remain as they were, and in due course of time even grow larger. This is evidence that the symptoms from which the patients suffered were not caused by the spurs but by other factors, such as myofibrositis, strained ligaments, diseases of internal organs, or true spondylarthritis which will be discussed later.

Another argument against the causal connection between the marginal spurs and the clinical symptoms commonly attributed to them is derived from the observation that roentgenograms of the spine of persons over 50 years taken shortly after an injury often reveal extensive lipping of the vertebral bodies which could not develop in the brief period between the injury and the roentgen-ray examination because this period amounts often only to a few days, sometimes merely to a few hours.

Last, not least, it is a common place experience that roentgenograms taken for diseases of the neck, chest or abdomen disclose numerous spinal exostoses while the patients do not have and never did have any complaints referable to the spine.

What has been said of the marginal spurs, fully applies also to the narrowing of the intervertebral space with which the spurs, in about 20 per cent, are associated. The flattening of the intervertebral disc in the course of the aging process is a painless process since no nerves are present in the discs (Jung and Brunschwig). Accordingly, even a highly pronounced narrowing of the intervertebral space by itself does not give rise to pain or any other symptoms.

The fact that the spinal exophytes and the flattening of the intervertebral disc are not pathogenic is in line with the previous statement that the marginal spurs rather than a pathological phenomenon are an adaptation of the intervertebral bodies to the physiological process of degeneration of the intervertebral disc.

There is an obvious analogy between the mode of the development and the appearance of the marginal spurs of the spine and those occurring in the

peripheral joints. The analogy is so far reaching that the condition has been called hypertrophic spondylarthritis or spondylarthritis deformans just as we speak of hypertrophic arthritis or arthritis deformans of the knees or hips. However, these terms have been criticized because as Oppenheimer has stated, "the articulation formed by two vertebral bodies and the inter-

FIG. 4. Narrowing of the intervertebral space between the fifth and sixth cervical vertebrae with marginal spurs on the anterior surfaces of the respective vertebrae. The corresponding apophyseal joint is narrowed, the contours are indistinct. Summary: destructive spondylosis and spondylarthritis ("discogenetic" spondylarthritis).

vening discs is an amphiarthrosis or symphysis," and "since the vertebral symphyses have no synovial membranes, no joint cavities, nor free articular cartilages, nor any other parts characteristic of synovial joints, the symphyses cannot be the seat of arthritis. Accordingly, says George, the term hypertrophic spondylarthritis should not be used. It has no foundation of fact, it is not accurate and it has no pathological basis to substantiate its use." It may be added that the term hypertrophic spondylarthritis if used to in-

dicate the presence of marginal spurs, is a misnomer also for another reason. The reason is that the marginal spurs are not the result of an inflammatory process, but a reparatory reaction of the vertebral bodies to the degeneration of the intervertebral discs. Under these circumstances the term "hypertrophic spondylarthritis" or "spondylarthritis deformans" should not be applied with reference to marginal spurs, because they are bound to confuse the physicians as to the nature of the condition and its treatment, and to spread fear and anxiety among the patients.

For the last few years we have been using, for lack of anything better, the term spondylosis to designate the presence of abnormal findings in the weight bearing structures of the spinal column. We speak of marginal spondylosis if spurs are present at the edges of the vertebral bodies, and of destructive spondylosis if a narrowing of an intervertebral space also is present. It may be emphasized that a narrowing of an intervertebral space in absence of pronounced marginal spurs, is not characteristic of spondylosis but is rather suggestive of a protrusion of the nucleus pulposus if it occurs in the lower cervical or lower lumbar spine. It seems that the degeneration of a displaced disc takes place faster than of one in normal position so that the vertebral bodies are lagging in the production of new bone.

In a minority of the cases, approximately in about 10 per cent of the patients showing spinal spurs, these findings are not due to the aging process but due to other factors, such as deformities, injuries, infectious and neoplastic processes. The mechanism leading to the formation of the marginal spurs in these cases is basically not different from that in the process of disc degeneration due to the advancing age. As a rule, however, the spurs are limited to one area, and are often solitary. The roentgenograms which demonstrate the presence of the spurs in such cases usually also disclose the underlying pathological condition.

II. Disorders of the Motor Function of the Spine (Spondylarthritis)

The intervertebral or apophyseal joints are the only true joints of the spine. They contain, as any joint of the extremities, a synovial membrane, two cartilagenous surfaces and a capillary space in which certain motions can be carried out. Radiographically the joint spaces appear as 1 to 2 mm. wide slits, sharply delineated by two parallel lines. The direction of the planes of the spinal joints is different in the various parts of the spine. In the cervical spine the joint spaces run in the anteroposterior direction and can be seen on lateral roentgenograms (figure 1). In the thoracic spine the joint spaces are turned in the frontal direction and can be visualized only on oblique views. In the lumbar spine the joint spaces are situated in the sagittal direction and can be seen both in the anteroposterior and oblique view. Of the two views the anteroposterior is less dependable because the planes of the lower lumbar vertebrae often instead of being situated sagitally

are turned more or less sidewards. In addition, even a slight scoliosis or rotation of the spine changes the position of the intervertebral joints. Therefore, when a joint space in its full length cannot be traced on the anteroposterior roentgenogram, oblique views from varying angles should be taken (figures 6, 10).

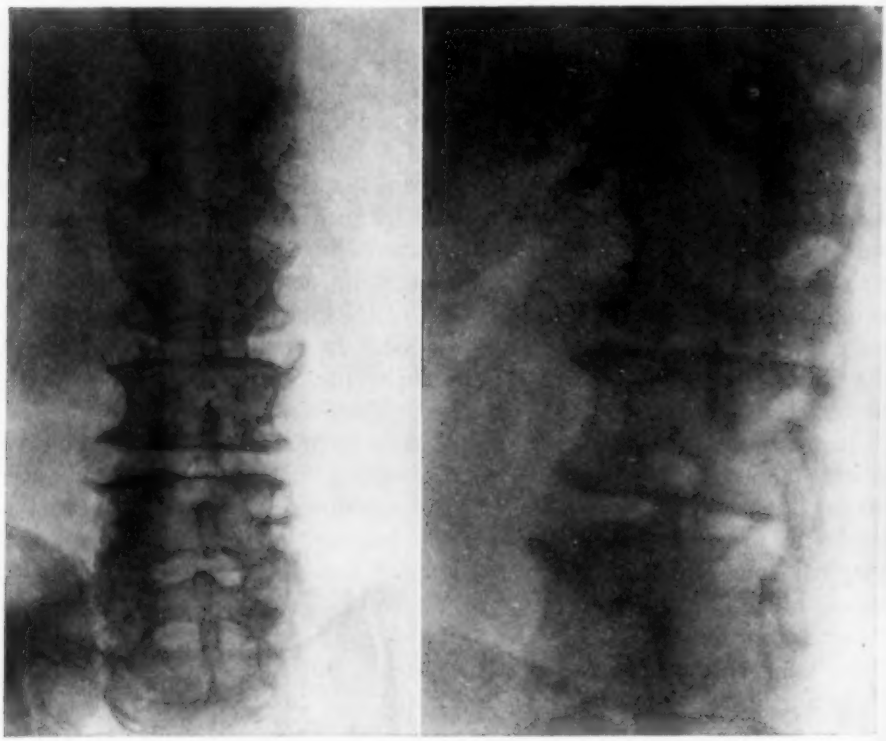

FIG. 5. (*Left*) Extensive marginal spurs in the lower lumbar spine.

FIG. 6. (*Right*) Same case as in figure 5. The apophyseal joints appear normal in the oblique view. Summary of figure 5 and figure 6: spondylosis, no spondylarthritis.

A true spondylarthritis can occur in the apophyseal joints, the only type of spondylarthritis unrestrictedly deserving this designation. Arthritis of any origin can develop. If we disregard the rare acute conditions caused by definite microörganisms, two main types of chronic spondylarthritis may be differentiated as they customarily are distinguished in the peripheral joints: the rheumatoid type and the osteoarthritic type.

Rheumatoid arthritis of the spine, also called Marie-Strümpell's spondylitis, predominantly affects young men. It is a systemic disease, which if not arrested, steadily progresses in the ascending direction until all intervertebral joints eventually show osseous ankylosis. Decalcification of the vertebral bodies and calcifications of the spinal ligaments are features accompanying the more advanced stages of the inflammatory process taking

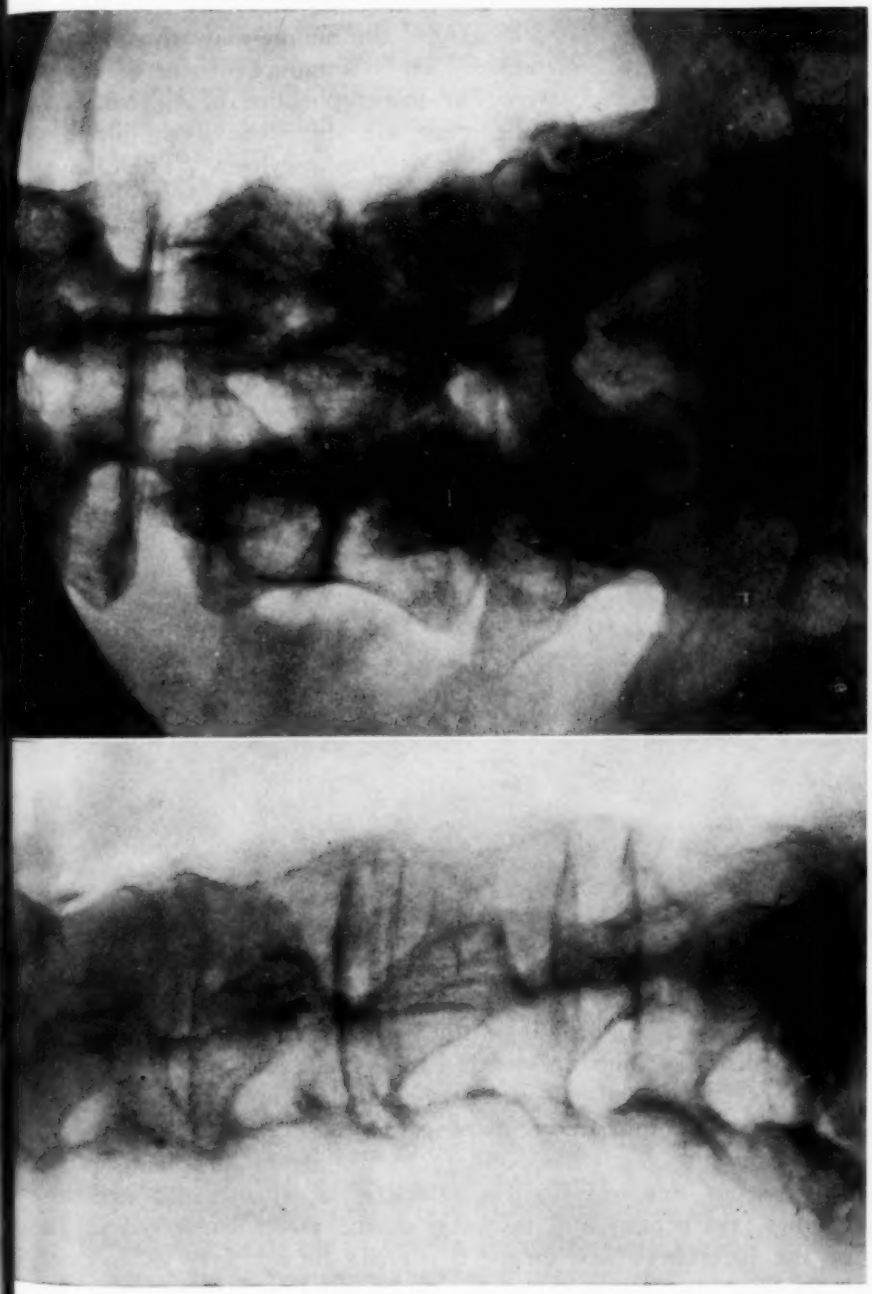

FIG. 7. (*Left*) Ankylosis of the apophyseal joints of the lumbar spine with beginning ossification of the corresponding spinal ligaments. Summary: spondylarthritis, rheumatoid type, no spondylosis.

FIG. 8. (*Right*) Condensation of the vertebral bodies of the lower lumbar spine around the apophyseal joints which appear narrowed.

place in the joints (figures 2, 7). The sedimentation rate of the red blood cells is, as a rule, increased.

Osteoarthritis of the spine is a disease of the middle and advanced age groups. It affects equally both sexes. It is a monoarthritic or oligoarthritic condition (figures 3, 9). The lower portions of the cervical, thoracic and lumbar regions of the spine are the sites of predilection. Osteoarthritis of the spine never causes an osseous ankylosis. The calcium content of the vertebrae is within normal range, except in very old individuals where it is reduced. The sedimentation rate of the red blood cells is normal.

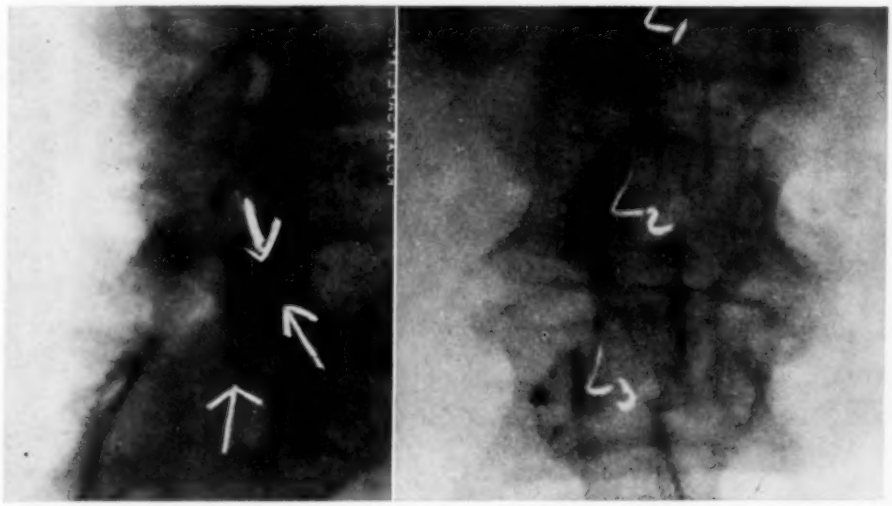

FIG. 9. (*Left*) Same case as in figure 8 seen in an oblique view. The apophyseal joints are definitely narrowed and show subchondral bone sclerosis. Summary of figures 8 and 9: spondylarthritis of the osteoarthritic type, no spondylosis.

FIG. 10. (*Right*) The upper three lumbar vertebrae with signs of marginal spondylosis. The intervertebral spaces and the apophyseal joints appear of normal width.

As to the local symptoms, swelling of the joints, a finding so valuable in the diagnosis of arthritic conditions of other localizations, cannot be noticed in the spine because the joints are covered by many layers of thick muscles. In both types of spondylarthritis there is backache, limitation of motion, pain radiating into the limbs, and tenderness on pressure to one side or both sides of a spinous process, corresponding to the joints affected. Radiographically, osseous ankylosis is characteristic of rheumatoid arthritis, marginal spurs, sharpening and thinning of the facets of osteoarthritis. Otherwise, the differences between the two types are not very pronounced. In both types the lumen can be narrowed to the point of its indiscernibility. The contours are blurred, often ragged and wavy. The subchondral bone is porotic in the initial stages and condensed in the later stages. The condensation may reach the stage of heavy sclerosis (figures 2, 3, 4, 7, 8, 9, 11).

III. Relationship Between Spondylosis and Spondylarthritis

As to the relationship between spondylosis and spondylarthritis, things are different in the two types of chronic arthritis of the apophyseal joints. No marginal spurs or narrowing of the intervertebral spaces occur in the rheumatoid type of spondylarthritis since the latter is a disease of young adults and no degenerative changes take place in the intervertebral discs at

Fig. 11. Same case as in figure 10 seen three years later. There is an increase of the marginal spurs. The intervertebral spaces and the apophyseal joints appear narrowed, the bone around the joints is condensed. Summary of figures 10 and 11: with the establishment of the destructive spondylosis signs of spondylarthritis, osteoarthritic type, develop ("discogenetic" spondylarthritis).

that age. Only when the patients reach the age at which the spurs normally develop, do they exhibit in addition to their spondylarthritis also signs of spondylosis. This indicates that even a highly pathologic process of the apophyseal joints as it occurs in rheumatoid spondylarthritis does not in any way accelerate the process of degeneration in the intervertebral discs. One is time and again surprised to see that even spines of the "bamboo" type showing osseous ankylosis of all spinal joints and complete ossification of the spinal ligaments show no marginal spurs and normal intervertebral spaces.

The contrary is true of osteoarthritis. Out of 43 cases with radiological signs of osteoarthritis only eight, thus about 20 per cent, showed no signs of spondylosis. Thus the vast majority of the patients afflicted with osteospondylarthritis also showed signs of spondylosis. This frequent coexistence suggests the possibility that spondylosis may be a factor in the development of spondylarthritis.

To clarify this problem we examined 92 cases showing marginal spondylosis, that is spurs without narrowing of an intervertebral space. Twenty-four patients of this group showed also radiological signs of osteospondylarthritis. Thus spondylosis was considerably more frequent than spondylarthritis. Only about 25 per cent of the patients with marginal spondylosis had also signs of osteoarthritis of the apophyseal joints. This ratio does not suggest that spondylosis favors the development of spondylarthritis, the more so since the site of the spondylosis often did not coincide with the site of the spondylarthritis. The coincidence of the two conditions in a certain percentage of cases is only natural in view of the fact that both occur in the middle and advanced age groups.

The ratio between spondylosis and spondylarthritis changes distinctly when we limit our attention to the cases with signs of destructive spondylosis, thus showing not only marginal spurs but also a narrowing of an intervertebral joint. Out of 23 cases of this type, 11, thus about 47 per cent, also showed signs of osteospondylarthritis. This is nearly twice the incidence found among the cases with marginal spondylosis. The occurrence of osteospondylarthritis is in this group even more frequent when we include cases without radiographic evidence of a joint disease which, however, had the clinical symptoms of osteospondylarthritis comparable to synovitis in the peripheral joints. In the course of the observation of such patients, we have seen cases which on the first examination were roentgenographically negative but turned out roentgen-ray positive some time later (figures 10, 11). It seems probable that the majority of the patients with a narrowing of an intervertebral space are likely, sooner or latter, to develop osteoarthritis of the apophyseal joints. This is in line with observations of Williams, Ayers and Oppenheimer.

The explanation of the connection between destructive spondylosis and osteospondylarthritis runs along the following line: when the degeneration of an intervertebral disc has advanced to a degree producing a narrowing of the intervertebral space, then the superior articular processus slips downwards and the congruence between the articulating facets of the apophyseal joints is lost. A state of irritation results which gradually leads to changes in the intervertebral joints, both in the synovia and the cartilage, causing backache and pain on moving the joints. The frequency of radiating pain is due to the proximity of the intervertebral joints and the intervertebral foramina which are traversed by the spinal nerves on their way to the limbs.

Thus, besides the idiopathic cases of osteospondylarthritis, in which the origin of the disease is as obscure as in osteoarthritis of many other localiza-

tions, there is a group of cases of "discogenetic" origin, to employ the terminology of Oppenheimer (figures 4, 11).

Summarizing, the connection between spondylosis and spondylarthritis may be explained as follows. Originally, spondylosis is an adaption of the vertebral bodies to the degenerative processes in the intervertebral discs. Spondylosis is not pathogenic nor arthrogenic as long as spurs are its only manifestation. In about 20 per cent of the cases the degeneration of the disc advances to a degree causing a narrowing of an intervertebral space. Once this stage is reached, spondylosis becomes a condition predisposing to spondylarthritis, or, as may be said, a prearthritic condition which, sooner or later, is likely to lead to the development of an osteoarthritis of the intervertebral joints.

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CASE REPORTS

MALIGNANT THYMOMA IN A CASE OF MYASTHENIA GRAVIS *

By Samuel E. Miller, Lt. Col., M.C., A.U.S., and Walter Redisch, Capt., M.C., A.U.S.

A case of myasthenia gravis occurring in a 21 year old soldier with a mediastinal mass which proved to be a malignant tumor arising from the thymus gland is reported. The reasons for reporting a single case are: the interesting but still poorly understood relationship existing between thymic tumors and myasthenia gravis; the fact that in the vast majority of cases, these tumors are non-malignant; and because of its military medical aspect in that any case of abnormal fatigability occurring in a soldier requires consideration of myasthenia gravis as a possible cause.

Case Report

A 21 year old white male soldier with one year of service was admitted to the hospital October 17, 1944 from his regimental dispensary. His first symptoms appeared during basic training. While doing manual of arms he noticed that his wrists gave out and he was unable to extend his arms. After he had rested for a while he was able to resume his activity. On his first march, after going a mile or two, his knees buckled and he had to sit down. After resting he was again able to proceed for a short while. He also noticed that on awakening in the morning he felt well, but became progressively more tired as the day passed. After two months of basic training, which he was unable to complete because of this weakness, he was sent to radio school. He had no great difficulty there because of the sedentary nature of the work. Two months later, upon completion of his course, he was returned to duty with his organization. The same symptoms promptly recurred. He was then placed on limited service and excused from arduous duties.

Early in October, 1944 he noticed that liquids and foods leaked out of his mouth toward the end of a meal. He also noticed that after talking for several minutes his speech became slurred and indistinct. Toward the end of the day he would notice diplopia.

Physical examination on admission revealed incomplete bilateral ptosis, profuse collection of saliva in mouth, and slurring of speech of fatigue type. Laboratory studies, including urinalysis, complete blood count, serology, glucose tolerance, basal metabolic rate, and stool examination for parasites and ova, were all negative. Chest roentgenogram revealed a marginated shadow of homogenous density in the anterior superior mediastinum, measuring about two inches vertically and one and one-half inches horizontally, with compression of adjacent lung tissue. Fluoroscopy revealed the mass to be pyramidal in shape, and not to pulsate or move on swallowing. The impression was a thymic tumor.

Upon examination the soldier was believed to have myasthenia gravis. Alleviation and aggravation tests, using prostigmine and quinine, respectively, were both

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strikingly positive. When given 10 grains of quinine by mouth the following phenomenon took place: About 30 minutes after medication he suddenly became very weak, his speech unintelligible, he was unable to swallow water, and he could not sit up. This was relieved promptly by injection of 1 c.c. of 1–2,000 prostigmine methylsulfate. For therapeusis he was administered 1 c.c. of 1–2,000 prostigmine methylsulfate hypodermically before meals with complete alleviation of symptoms. This enabled him to eat his meals without difficulty. His speech became clear and articulate within 15 to 20 minutes after injection. Although his symptoms showed progression during his hospital stay, especially in his facial mimic and deglutition muscle groups, increased doses of prostigmine were able to compensate.

Because of reports of similar cases in which removal of thymic tumors had resulted in marked improvement of the clinical picture of myasthenia gravis, he was transferred to a thoracic surgery center November 28, 1944 for consideration of operation. After his transfer the medication had to be increased to 1 c.c. of 1–2,000 prostigmine methylsulfate every three hours. The indication for operation was concurred in at the thoracic surgery center and an operation was performed December 9, 1944. A median sternotomy was performed and a firm, lobulated tumor occupying the region of the anterior mediastinal space and extending both to the right and to the left and up into the neck was found. No definite capsule was present, except in a few areas, and the tumor appeared to invade most of the adjacent structures. Three large parts were removed separately but the mass in the right lateral region was left in place as it was obvious that the tumor was malignant and could not be totally removed.

Immediately after operation the patient's condition was good but great difficulty was encountered in keeping the tracheobronchial tree clear of secretions. Frequent aspirations were necessary. On the evening of the third postoperative day breathing became very difficult and the patient died.

The essential findings on autopsy were: an apparently malignant tumor of the thymus gland which infiltrated the pericardium; atelectasis of the left lower lobe due to bronchial obstruction from mucus; and cerebral edema.

The clinical diagnosis of myasthenia gravis was borne out by histological findings. Microphotographs 1 to 5 illustrate the histopathology of the tumor and of the striated muscle lesions.

Discussion

Since Laquer and Weigert [1] first called attention to a suspected relationship between thymic hyperplasia and myasthenia gravis in 1901 much interest has been shown in developing a better knowledge of this syndrome. The assumption that the presence of thymic pathologic lesions in connection with clinical myasthenia gravis may be more than a mere coincidence seems to be supported by the following facts:

1. According to literature,[2, 3, 4] 50 to 80 per cent of all cases of myasthenia gravis coming to necropsy have shown pathologic changes in the thymus varying from simple hyperplasia to true tumors. These tumors of the thymus, as described in the literature, have practically always been benign.[5, 6] The first case in which a malignant thymic tumor was described in connection with myasthenia gravis was published in 1908.[7] Since that date, however, in one series of 95 cases,[8] six were reported as having malignant thymomas. One authority on the subject [9] has expressed the opinion that the association of malignancy of the thymus gland and of myasthenia gravis is not as rare as it is thought to be.

2. Two investigators in 1945 found the incidence of myasthenia gravis in cases of thymoma to be nearly 100 per cent.[10]

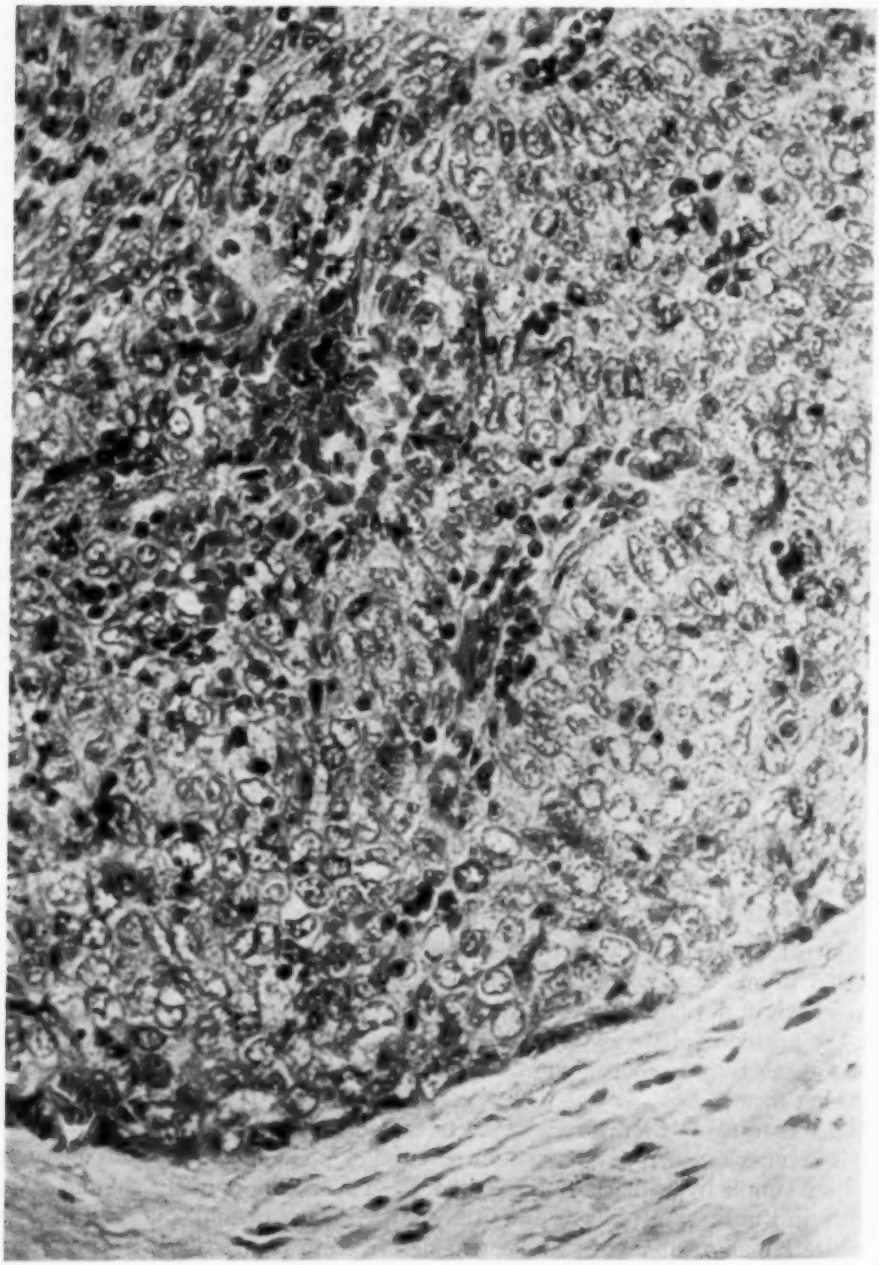

FIG. 1. Section through the primary malignant thymic tumor. Most of the cells in this section are large polygonal cells with pale vesicular nuclei. In some places they are hyperchromatic and spindle-shaped. These cells tend to assume a palisade arrangement. Occasional mitotic figures can be seen. Scattered cells resembling "lymphocytes" (thymocytes) are seen throughout the section. No form of differentiation to Hassell's corpuscles can be discerned. This portion of the tumor shows what appears to be a capsule. U. S. Army Medical Museum Negative No. 88069.

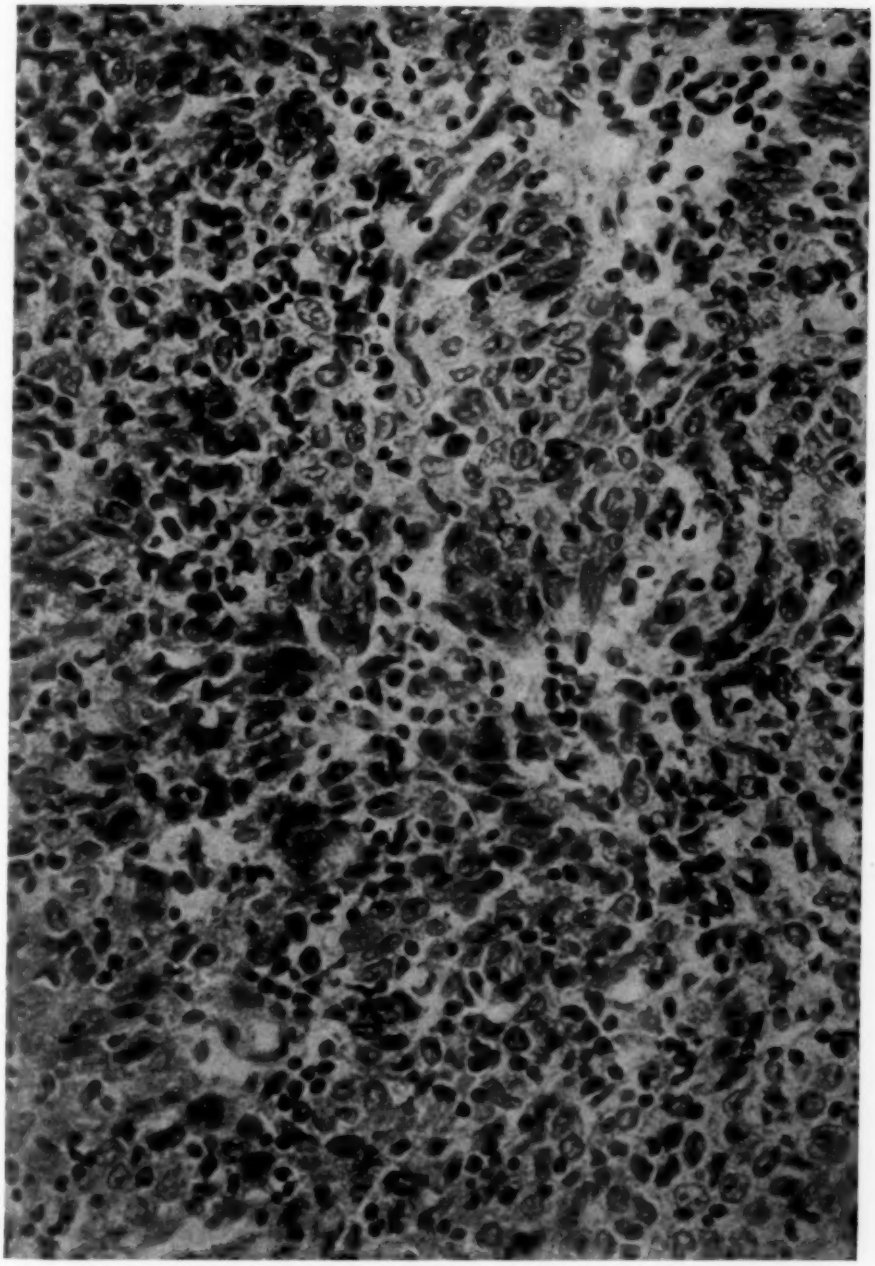

FIG. 2. Section through the tumor which is very similar to figure 1. The tendency to palisade arrangement of the hyperchromatic cells is more marked. U. S. Army Medical Museum Negative No. 88072.

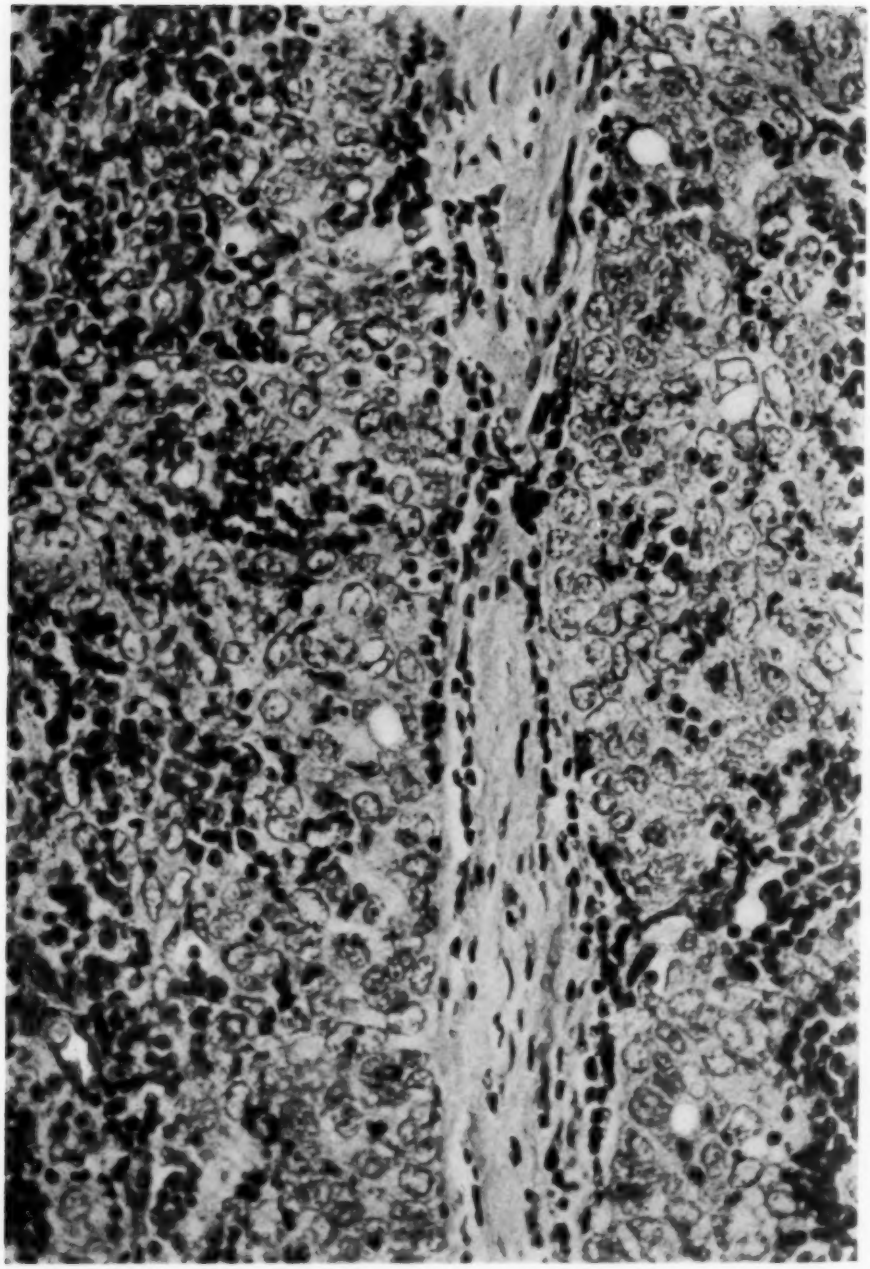

FIG. 3. Section through tumor showing small thymocytes which are more numerous in this section than in the others. The tumor cells are almost all of the large, pale, vesicular type and closely resemble reticulum cells. No palisade arrangement and no structures resembling Hassell's corpuscles can be discerned. U. S. Army Medical Museum Negative No. 88071.

FIG. 4. Section of skeletal muscle showing very large, dense focus of lymphorrhagia. Such lymphorages are characteristic lesions of myasthenia gravis. U. S. Army Medical Museum Negative No. 88073.

FIG. 5. Perivascular collection of lymphocytes in skeletal muscle. U. S. Army Medical Museum Negative No. 88068.

3. The relationship is further supported by therapeutic results achieved through thymectomy in cases of myasthenia gravis. Since the first such attempt in 1913,[11] several such reports have appeared all over the world. In this country there are reported several instances in which myasthenia has been alleviated by thymectomy.[12, 13] Although results have not been completely successful and the possibility of spontaneous remissions has to be considered, the over-all evidence seems to be in favor of operation whenever a definite thymic tumor can be demonstrated.

4. The syndrome has been produced experimentally by repeated implantation of infantile thymus into dogs. The resulting picture of myasthenia gravis was then alleviated by the administration of prostigmine.[14]

Discussion of the physiology of the mechanism involved and of the aspects of modern therapy appears unnecessary here as it has recently been excellently presented.[13]

From a military standpoint this is a case which illustrates the necessity for proper consideration and evaluation of subjective complaints. Failure to do so might result in the unfortunate labeling of a sick man as a "goldbrick." It appears that two factors may have contributed to failure of early recognition of this man's condition: (1) Insufficient attention was paid to his subjective complaints; and (2) the rather innocuous early symptoms, that is abnormal muscle fatigability with obvious recovery on rest, were not properly evaluated.

Summary

1. A case of myasthenia gravis with malignant tumor of the thymus is reported.

2. The relationship between pathologic lesions of the thymus and the clinical picture of myasthenia gravis is discussed.

3. The military medical aspect of the case is considered.

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PRIMARY AMYLOIDOSIS: REPORT OF A CASE*

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ONLY in recent years has there been some unanimity of opinion in regard to the classification of amyloid disease which is divided into primary amyloidosis, secondary amyloidosis, amyloid associated with multiple myelomata and tumor-like formation.

Primary amyloidosis is subdivided into the systemic and localized types in which some variation occurs. It was first described in 1856 by Wilks,[1] but is still poorly understood, and of unknown etiology. In 1936 Kerwin[2] reported two cases and in 1939 Koletsky and Stecher[3] made a comprehensive review of the literature noting some 30 cases, 22 of which were of the systemic type. They also added one of their own. Their series did not include the case of Larsen[4] or that of Budd,[5] nor the two cases reported by Kerwin.[2] Since then single cases have been reported by Binford,[6] and by Sappington, Davie and Horneff.[7] Pearson, Rice and Dickens[8] have reported two cases and Dillon and Evans[9] three cases, making a total of 44 cases.

Considerable emphasis has been placed on the tendency of primary amyloidosis to involve the mesodermal tissues, especially the skeletal and smooth muscles of the cardiovascular and gastrointestinal system, whereas in the secondary type, the liver and spleen are chiefly involved. Importance has also been attributed to the atypical staining in the primary form in contrast to the uniform staining in the secondary type, which suggests that the two types are not chemically identical.

The Bennhold Congo red test when completely positive is practically pathognomonic of this disease. If the possible presence of amyloidosis is kept in mind, the clinical findings, which have been more fully described in recent years, should suggest the diagnosis. The verified presence of amyloidosis is important from the point of view of prognosis.

CASE REPORT

W. A. J., a 58 year old male, on January 31, 1942 complained of swelling of the ankles for about three months. The family history was irrelevant. He had had measles, mumps, chicken pox and typhoid fever. His general health, however, had been excellent; and he had not experienced any operations or injuries. He worked in the printing department of a large firm but did not come in contact with lead. There was contact with cleaning fluid frequently. He was a total abstainer from

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alcohol and tobacco. In the present illness there were no symptoms referable to the circulatory system except edema of the ankles. The respiratory system was negative. His appetite was poor owing to slight digestive upsets at times. There were no symptoms of urinary tract disease, except for the discovery of albumin in the urine two months before admission.

On physical examination the important findings were as follows: Ears were negative. The pupils reacted normally and there was no icterus of the conjunctivae. In the ophthalmoscopic examination a patch of choroiditis was noted in the right eye near the disc. The examination of the nose, teeth, tonsils, tongue, and neck was negative. Lungs were clear. The cardiac dullness extended 8 cm. to the left of the mid-line in the fifth interspace. No shock or thrill was palpated. The cardiac rate was 115; and the rhythm regular. No murmurs were heard. There were no prominent veins on the abdomen. The liver edge extended two fingers' breadth below the costal margin and liver dullness was 5 cm. below it in the mid-clavicular line. The edge was sharp and smooth and there was no tenderness. Splenic dullness was increased and the spleen was easily palpable and thought to be moderately enlarged. The kidney regions were negative on palpation. The upper extremities were negative. In the lower extremities there was pitting over the tibia of both legs. Veins were slightly prominent. Reflexes were normal. The genitalia were negative. There was pitting over the lower lumbar and sacral regions, posteriorly. Height 5′ 5¼″; weight 155½ lbs.; temperature 98.2°; blood pressure, systolic 94, diastolic 74.

The laboratory findings were as follows: Hemoglobin 13 gm., red blood cells 4,510,000; white blood cells 6,400; differential count, polymorphonuclears 67 per cent, lymphocytes 35 per cent, monocytes 3 per cent, basophiles 1 per cent. The cells were normal in size and shape and a few platelets were present. The blood did not coagulate readily. Sedimentation rate: First 15 minutes 25 mm., one-half hour 41 mm., 45 minutes 50 mm., one hour 51 mm. (corrected 46 mm.) (Wintrobe). Blood sugar, two hours after breakfast, was 106 mg. per 100 c.c. Urine was dark amber, specific gravity 1.028, alkaline, pH–6, negative sugar, four plus albumin. Microscopically there was an occasional pus cell, a few casts and few phosphate crystals. Kline exclusive test for syphilis: negative.

Fluoroscopic examination of the chest: Apices and lung fields were clear. The hilus shadows were slightly increased on the right. Diaphragm action was normal. The heart and aortic shadows were within limits of normal.

Electrocardiographic findings: Auricular and ventricular rate 105; rhythm regular; PR interval 0.16 sec.; QRS duration 0.04 sec.; voltage, total in 3 limb leads 11 mm.; slight slurring of QRS complex in Leads I, II and notching in Lead III; ST segments isoelectric; T_1 upright and normal, T_2 upright and slightly low, T_3 slightly inverted, T_4 upright and normal.

On February 3, 1942, he was sent to the Columbia Hospital for further laboratory studies which were as follows: Blood urea 29.98 mg. per 100 c.c.; prothrombin time 40 sec. (Quick); coagulation time 4 min.; bleeding time 8½ min.; blood platelets 300,000; serum albumin-globulin ratio: albumin 3.6 per cent, globulin .9 per cent, total proteins 4.5 per cent. This was repeated eight days later and the albumin was 3.8 per cent, globulin 0.9 per cent, total 4.8 per cent. Sedimentation rate: first 15 min. 40 mm.; 30 min. 46 mm.; 60 min. 52 mm. The urine was acid, specific gravity 1.002, three plus albumin, negative sugar, occasional granular cast, a few pus cells, a few epithelial cells. Quantitative albumin was three grams per liter. Urine was negative for bile. An intravenous phthalein test showed 44 per cent output in the first 20 min., and 18 per cent in the next 20 min. The following blood pressure readings were made: February 4: systolic 110, diastolic 74; February 6, 112/72; February 8, 110/68; February 9, 110/62; February 11, 108/70; and February 14, 110/64. Impression at this time was a tubular nephritis and possibly an early cirrhosis of the liver. During

his stay in the hospital he was placed on a high protein, salt free diet, and given Lextron and amino acids. He left the hospital on February 16. The edema had diminished considerably and he felt stronger.

On March 6, 1942 he became mentally upset, had a slight chill and fever of 100.3° F. He returned to the hospital for 10 days. The fever lasted only three days and he soon became rational again. The blood pressure remained about systolic 110 and diastolic 72. The liver was still palpable two fingers' breadth below the costal margin and the spleen was also palpable. The edema was practically gone. Laboratory studies showed a hemoglobin of 80 per cent, white blood cells 11,000, polymorphonuclears 84 per cent, lymphocytes 15 per cent, L mononuclears 11 per cent. Blood urea was 49.96 mg. per 100 c.c. Urine was acid, specific gravity 1.018, one plus albumin, negative sugar, occasional pus cell and occasional granular cast. He was dismissed on March 16. The diagnosis remained the same.

After returning home he continued to improve to some extent. The Lextron was kept up and multiple vitamins added. The edema varied. Theobromine sodium salicylate was used without much success and later the edema became so marked that he was again admitted to the hospital on August 10, 1942. There was some ascites present but no enlarged veins on the abdomen. The liver was three fingers' breadth below the costal margin, easily palpable. The lower extremities were moderately edematous. Several blood pressure readings were made which averaged systolic 110 and diastolic 73. Laboratory studies at this time were as follows: Hemoglobin 80 per cent, white blood cells 14,000, polymorphonuclears 74 per cent, lymphocytes 26 per cent. Blood urea was 34.96 mg. per 100 c.c. Urine was acid, specific gravity 1.010, albumin 4 plus, negative sugar, occasional waxy cast, occasional blood cell, few pus cells. Blood protein could not be determined on account of the milky appearance of the serum. Unfortunately, lipoids could not be determined. He was now placed on a diet of protein 110 gm., fat 50 gm., carbohydrate 200 gm., and salt free. Digitora was given for a short period of time. Ammonium chloride 90 grains a day was given for three days, followed by salyrgan-theophylline 1 c.c. The salyrgan was given from then on every four days with ammonium chloride the day before and the day of each dose until the edema cleared. He left the hospital on September 7. Improvement continued at home, and he was able to walk short distances.

One month later he was sent to Johns Hopkins Hospital with the diagnosis of nephrosis, probably lipoid, and an unexplained enlargement of the liver and spleen. He was admitted on October 5, 1942 on the service of Dr. Louis Hamman. The laboratory studies were interesting and were as follows: Oct. 6, 1942, Serologic tests for syphilis in the blood: Flocculation test negative; blood slide test negative. Blood count: Red blood cells 5,130,000; hemoglobin 15 gm. (103 per cent), volume of packed red cells 41.7 per cent. White blood cells 7,150; volume of packed white cells 0.9 per cent. Sedimentation rate 49.0 mm. 1 hr., corr. 39.0 min.; icterus index could not be read. Mean corpuscular volume 81, mean corpuscular hemoglobin 29, mean corpuscular hemoglobin concentration 36, moderate anisocytosis. Differential count: Segmented neutrophiles 85 per cent, eosinophiles 2 per cent, basophiles 1 per cent, lymphocytes 4 per cent, monocytes 8 per cent. Blood analysis: serum non-protein nitrogen 30 mg. per cent, globulin 2 gm. per cent. Stool examination: Occult blood (Guaiac), Oct. 8, 1942: 3+. Total protein in urine in 24 hours 11 gm.; basal metabolism −3 per cent. Test satisfactory. Oct. 9, 1942: Stool examination: Occult blood (Guaiac) +. Bromsulfalein retention: serum too cloudy to read, probably a trace of retention. Blood analysis: non-protein nitrogen 40 mg. per cent, blood urea nitrogen 24 mg. per cent, urea clearance No. 1, 39 per cent normal standard clearance; urea clearance No. 2, 38 per cent normal standard clearance. Oct. 10, 1942: Fishberg concentration test: 1.022 (7 a.m.), 1.020 (8 a.m.), 1.015 (9 a.m.). Stool examination: No gross blood or pus present. Occult blood (Guaiac) ++.

Search for parasites fruitless. Urine: Dark-field examination of centrifuged specimen showed no doubly refractile bodies. Stool culture: No typhoid-dysentery group found. Oct. 12, 1942: Phenolsulfonphthalein excretion: one-half hour, 30 per cent; one hour, 10 per cent; two hours, 10 per cent: total, 50 per cent. Prothrombin time: Patient, 13 seconds. Normal control, 14 seconds. Blood analysis: Calcium 8.4 mg. per cent, phosphorus 3.8 mg. per cent. Refraction index too cloudy to read. Hippuric acid test: 1.68 grams hippuric acid excreted over 1 hr. period. Normal: 1.0 to 1.4 grams. Vitamin A determination: Carotene, .25 mg. per cent, A, 1.72 L.U. $\times 10^3$, Normal: 1.48 — 3.30 L.U. $\times 10^3$. Oct. 13, 1942: Cholesterol: total 449 mg. per cent, esters 322 mg. per cent. Oct. 14, 1942: Platelets 230,000. Smear also showed platelets normal in number. Oct. 5, 1942: Urine analysis: 1.015, clear alkaline reaction, no sugar, albumin ++++, Slight sediment containing an occasional white blood cell, no red cells. A few hyaline and waxy casts. Oct. 12, 1942: Sulkowitch test negative. Oct. 13, 1942: Clotting time 11 minutes.

There were several consultations and on Oct. 10, 1942 Dr. J. E. Howard made the following notation: "anasarca, albuminuria, excessive without red blood cells and with only few casts, marked hypoproteinemia with altered A/G ratio, greatly elevated blood fat—all point to nephrotic syndrome. Why the enlarged liver and spleen? Could the hypercholesterolemia induce by necessity xanthomatous changes in liver and spleen? Probably anything that will produce low serum proteins with albuminuria would raise the cholesterol. I don't know the answers to these questions but believe most likely is chronic glomerular nephritis in nephrotic phase. Amyloid, xanthomatosis, lymphoma seem far less likely. Dr. Fleischmann will do fractionated cholesterol for us." Oct. 9, 1942 Dr. Longcope wrote: "There is still very marked anasarca, edema of conjunctivae, of the scrotum and of the penis. His color is a remarkable pallor without the slightest yellow tinge, and yet he apparently has no anemia. There are several purpuric subcutaneous hemorrhages, particularly where he has been stuck with needles. No bleeding from gums or nose. Other striking features are edema of retina, patch of choroiditis on the right, rather small area of cardiac dullness without changes in sounds; extensive dullness and suppression of breath sounds at both bases posteriorly, ascites and readily palpable liver and spleen without noticeable enlargement of superficial veins over abdomen without bruits in the epigastrium; low blood pressure and comparative comfort. I think he has not only degenerative disease of the kidneys but of the liver, the etiology of which is, of course, completely obscure. Although amyloid disease is possible it is certainly not probable." He was discharged on Oct. 14, 1942 and the following day Dr. Hamman wrote me his impression which was as follows: "There can be no doubt that Mr. J. has chronic nephritis of the so-called nephrotic type. I never have seen an instance with as profound a disturbance of fat metabolism. The amount of fat in the blood is astonishing and the cholesterol in the blood is in the neighborhood of 600 mg. per 100 c.c. Some of the men in the laboratory are working on the fat and I hope later they may be able to give us the proportion of cholesterol in the form of esters. This has no practical importance but is an interesting detail. As a rule these cases in adults gradually go on to the development of renal function impairment with hypertension and later elevation of the non-protein nitrogen of the blood. In Mr. J. this stage has not been reached for his blood pressure is at a normal level as is also the non-protein nitrogen of the blood. The phthalein output seems to be a little reduced, namely about 50 per cent in two hours. The urea clearance test is rather low but it was not altogether owing to the large amount of fat in the blood. This much is quite clear and were that all, the situation would not be in any way puzzling. However, I cannot give a clear explanation for the enlargement of the liver and spleen. It is of course desirable to explain all of these abnormal findings on a single basis, therefore the first suggestion is that Mr. J. may have amyloid disease. This is a

possibility that I think cannot be definitely excluded and yet in my opinion the evidence is against it. It is impossible to do the Congo red test on account of the difficulty in reading the dye concentrations with so much fat in the serum. I am told we might have removed the fat from the serum and in that way made a satisfactory reading. Whether or not that is technically possible I cannot say. At any rate, the Congo red test is by no means a conclusive one but only suggestive. There has been much speculation about every possibility. One suggestion was that he might have universal xanthomatosis with involvement of the internal organs and not of the bones. This, I think, is a rather fantastic suggestion. I never have heard of such a condition and it seems to me altogether unlikely. This really is as far as I can go. I had a number of the men on the staff see Mr. J. to get their reaction and no one was able to add any suggestion of importance; only speculation with little fact to support it. I see nothing to do but proceed with the treatment of the nephritis and to ignore the other findings. There must be some degenerative disease of the liver and spleen but what it is I am unable to say."

A few days after he returned home he became very much more edematous. It was necessary at this time to use ammonium chloride and salyrgan-theophylline intravenously in 1 to 2 c.c. doses in order to get the edema cleared up. He was kept on Lextron as it had always been beneficial and was given multiple vitamins. As time went on he became thinner, weaker and was unable to retain food. He returned to the hospital on April 7, 1943. Examination revealed some ascites, the liver was a hand's breadth below the costal margin and the edge was sharp and smooth. The spleen was easily palpable. The lungs contained a few basal râles and the heart sounds were rapid and distant. There was no elevation of temperature. The laboratory findings were interesting: Hemoglobin 65 per cent, red blood cells 3,320,000, white blood cells, 9,000, polymorphonuclears 73 per cent, lymphocytes 27 per cent. The prothrombin time was 13 sec., and blood urea 179.88 mg. per cent. Urine was acid, 2 plus albumin, negative sugar, occasional granular cast, occasional pus cell and epithelial cell. There was no jaundice, but 500 c.c. of 15 per cent glucose were given intravenously daily for the nausea and to improve liver function. The course was rapidly downward. The heart sounds became weaker and more rapid, blood pressure remained about systolic 110 and diastolic 62. The temperature remained normal until the last three days when it went to 99.1 degrees. Pulmonary edema developed and he died on April 17, 1943. Although a definite diagnosis besides a nephrosis was not made, primary amyloidosis was still thought to be the most likely thing.

Autopsy was performed by Dr. H. H. Plowden with the following findings: "The body was that of a well developed and moderately nourished white man approximately 55 years of age, with prominent distention of the abdomen, and with considerable subcutaneous edema of the lower extremities. There was a marked general pallor of the tissues. At the request of the family, only the organs of the abdominal cavity were examined. In this cavity were 2,000 c.c. of straw-colored fluid, which escaped when the cavity was opened. The liver was approximately one and three quarters times its normal size, and extended downward two and one-half inches below the costal margin. This organ had a perfectly smooth glistening surface and rounded smooth margins and edges. Its color was a peculiar hard-to-describe pale pinkish waxy to glassy one. On gross section, the tissue of the organ cut with ease, and its internal color was the same as that of the surface. The tissue was intensely friable and gave the definite impression that it was infiltrated by some pathological process. Ordinary gross liver architecture could not be seen, aside from the larger divisions of the portal veins. The spleen was about five times the normal size, and was of the same color and texture and friability as already described for the liver. When gross sections of the spleen were removed and laid side by side with sections of the liver, they were no longer definitely distinguishable. They actually looked, felt and cut like sections of tissue from the same organ. The kidneys were of a

light pink color, glistening to waxy in appearance, and had a rough, very coarsely granular outer cortical surface. The capsules stripped easily, and the usual gross landmarks of the organ were obscured by some type of pathologic infiltrate similar to, but lighter in color than that already described in the liver and spleen. The gastrointestinal tract, the adrenal glands, the prostate, the urinary bladder, and the gallbladder, were all approximately normal in appearance. Diagnosis: Amyloidosis of liver, spleen and kidneys. Tissue was removed for microscopic study from the liver, the spleen and the kidneys. Study of these sections shows substantially the same picture inasmuch as there was present in all sections varying amounts of the peculiar protein-like material known as amyloid. In the liver practically the entire normal structure of the organ had been destroyed, and the only liver cells remaining were occasional irregular, rather long cords of liver cells, made up of single liver cells placed end to end. In between these occasional cords of liver cells were very heavy masses of amyloid, which are pale pink staining, perfectly smooth and homogeneous, without any granularity whatsoever, thus giving a peculiar glassy appearance to most of the sections. Microscopic sections from the spleen showed substantially the same picture, except that, if possible, more amyloid was present in any given area than in the liver. There was practically no remaining splenic pulp. An occasional single splenic pulp cell could be found, and other than these, there remained only the blood vessels and previously formed supporting fibrous connective tissue framework. In the kidneys the amyloid material was not nearly so plentiful as in the two organs previously described. Here it was present only in the glomeruli and their capsules, which were almost entirely destroyed by its infiltrating and compressing qualities. Diagnosis: Amyloidosis of liver, spleen and kidneys."

Comment

The reported case is of particular interest for two reasons:

1. Because only a few cases of primary systemic amyloidosis showed such marked involvement of the liver, spleen and kidneys though these are commonly involved in the secondary type.

2. Because death was due to heart failure and azotemia. Of the 44 cases reported in only five was death attributed to the heart, very few had the nephrotic syndrome and only one had a true azotemia.

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PALINDROMIC RHEUMATISM *

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SINCE the publication of the description of palindromic rheumatism as a "'new,' oft recurring disease of joints apparently producing no articular residues" by Hench and Rosenberg,[1, 2] several additional case reports have appeared in the literature.[3, 4, 5, 6, 7, 8] However, because of the apparently infrequent occurrence of this condition, it is believed appropriate that we record our observations of a patient in whom the diagnosis of palindromic rheumatism seems well established in accordance with the description presented by Hench and Rosenberg.

Briefly, palindromic rheumatism is characterized by recurrent attacks of pain, swelling, redness, and disability generally of only one, but occasionally of more than one, small or large joint. The symptoms and findings generally last only a few hours or days and disappear rather rapidly to recur repeatedly at irregularly spaced intervals with no demonstrable residual joint changes. Constitutional reactions in the form of fever accompanying the attacks are unusual, but may definitely occur.[9] Laboratory tests including roentgenographic examinations of affected joints after numerous attacks reveal no persistently significant abnormal findings. The history, symptoms and findings of palindromic rheumatism are usually definite enough to permit a differentiation from other articular diseases such as rheumatoid arthritis, periarticular fibrositis, intermittent hydrarthrosis and rheumatic fever. A more difficult differentiation is that between the conditions described as "angioneural arthrosis" by Solis-Cohen [10, 11] or "allergic rheumatism" of Kahlmeter [12] and palindromic rheumatism. For a discussion of the similarities and differences the reader is referred to the discussion by Hench and Rosenberg.[2]

The etiology of palindromic rheumatism is still in doubt. Allergy, infection, and psychogenic factors have been suggested without any substantiation. Some patients believe that physical activity precipitates attacks. Our patient was of this opinion, hence was permitted to push a lawn mower. After two days of such activity he did develop pain, redness, and swelling of the metatarsophalangeal joint of the left great toe. However, attempts to precipitate other attacks by equally vigorous physical activity proved unsuccessful.

Inasmuch as definite etiological factors are not known Hench and Rosenberg [2] proposed the present designation for the disease as being a satisfactory descriptive term. They believed the term "rheumatism" preferable to "arthritis" in that it is more inclusive thereby being more applicable to not only the arthritis which occurs, but also to the periarthritis, para-arthritis, and the occasional subcutaneous nodules which may be features of the disease. The word, palindromic, was derived from the Greek and means literally "to run back" or "recurring" or "returning."

No uniformly effective therapy has been found for this condition. Removal of foci of infection and use of vaccines, bee venom, epinephrine, ephedrine, amphetamin, ergotamine tartrate, histaminase, histamine desensitization and diets low in purines or free of suspected food antigens have not been effective. Some patients feel that relief from nervous fatigue brings about improvement.

* Received for publication January 17, 1946.

In the series reported by Hench and Rosenberg, 15 per cent of the patients became well, 44 per cent improved somewhat, 26 per cent remained the same, 11 per cent became somewhat worse and one patient died of an urelated illness. Apparently the only definite prognostic information one can give in any given case is the fact that no residual joint changes will result, for in spite of thousands of attacks in the series of patients reported by Hench and Rosenberg, not a single joint has demonstrated permanent changes.

Case Report

A 31 year old enlisted man entered the hospital because of swelling of the joints of his right thumb for six hours. This swelling had come on rather suddenly and was associated with redness, pain and slight limitation of motion of the affected joints. The patient stated that he had had many similar attacks during the past 13 years.

The first attack of pain and swelling was noted in 1932 when the patient, while working on a farm, developed pain, redness and swelling of the right first metatarsophalangeal joint. He thought the swelling was due to walking on rough ground while plowing and did not seek any medical attention. The swelling subsided in about two days, leaving no pain or deformity. Approximately three weeks later he developed a similar swelling of the left index finger which subsided just as promptly without medication.

Since May, 1932, the patient had had frequent attacks of pain, redness and swelling about various joints of the body. These attacks came on in a few hours or a day and left just as promptly, usually lasting two to three days. He estimated that during the past 13 years, he had had over 300 such attacks. Usually only one or two joints were involved during an attack; however, he remembered one attack during which all the joints of the fingers of the left hand were involved at one time. The symptoms were never severe enough to incapacitate the patient, although they interfered with his efficiency in getting about in the performance of his work.

The patient's past history revealed that he had had malaria in 1934 and gonorrhea in 1936 with no apparent sequelae. He denied any history of hay fever, asthma, or other allergic disease. There was no history of articular disease in the patient's family; no familial history of allergy or tuberculosis was elicited. The patient's father was 60 years of age and was well. His mother died at the age of 57 because of "stomach trouble." The wife, two brothers and three sisters of the patient were in good health.

The patient was reared on a farm in East Texas and at the time of his coming into the Military Service was employed as a worker in the oil fields doing strenuous physical work. He had been in the Army for five years and had been assigned to the Air Corps within the Continental United States during his service.

Physical examination of the patient on admission revealed a well-developed, well-nourished, white male who did not appear acutely uncomfortable. The temperature was 98.4° F.; the pulse and respiratory rates were within normal limits. The blood pressure was 108 mm. Hg systolic and 68 diastolic. The tonsils were atrophic, the teeth revealed no abnormalities. There was no evidence of sinus disease. The hearing was diminished to 6/15, bilaterally, by the whispered voice test. Examination of the ears revealed no abnormalities; no tophi were noted.

Moderate edema and redness of metacarpophalangeal and interphalangeal joints and the surrounding soft tissues of the right thumb were noted (see figure 1). There was slight limitation of motion of these joints as a result of the swelling. These findings remained for approximately 36 hours, then subsided gradually leaving no sequelae.

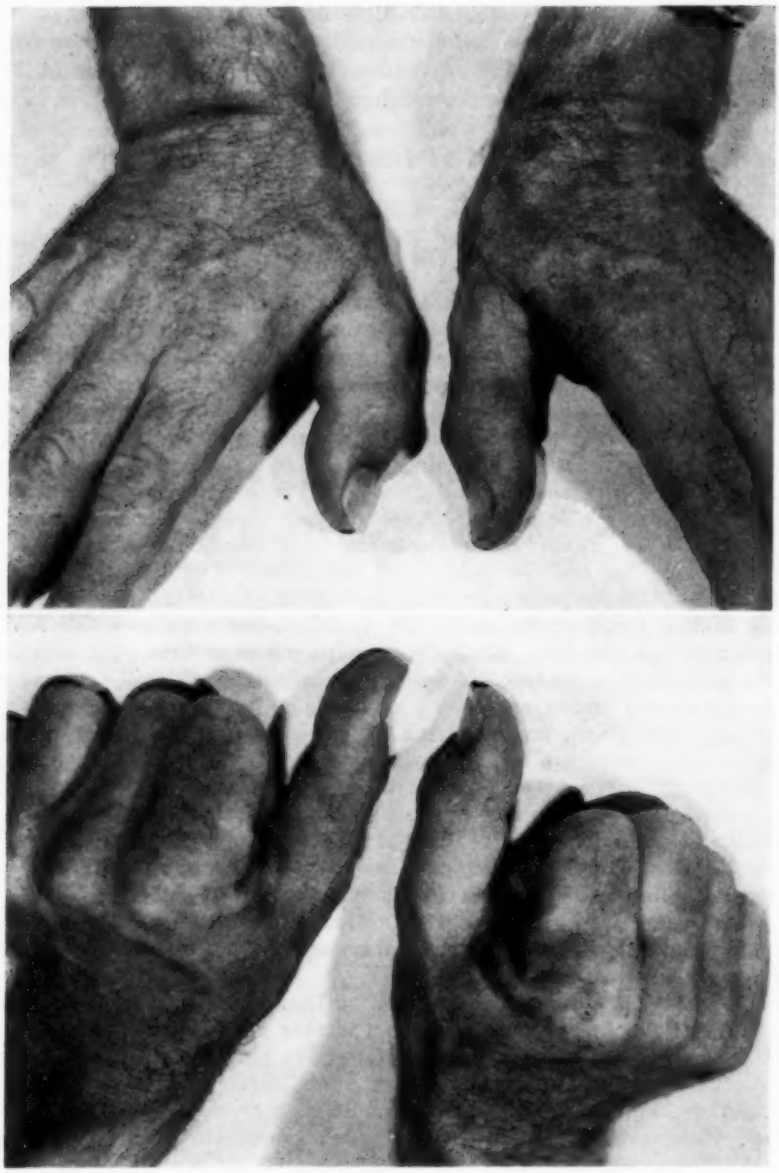

FIG. 1. Two views of the hands during an attack. Note the swelling of the right thumb, particularly about the interphalangeal joint.

One of us has observed this patient during two other attacks. On one of these occasions the left first metatarsophalangeal joint was red, swollen and painful for approximately 24 hours, and during another attack, the distal interphalangeal joint of the left index finger was similarly involved for approximately 48 hours. The temperature, pulse and respirations were normal during these attacks, and the patient complained of no constitutional reactions.

The laboratory reports revealed no abnormalities of definite significance. The red blood count during the attack was 4,976,000; the hemoglobin was 85 per cent. The white blood count was 7,500, the differential count showing 52 per cent neutrophiles, 28 per cent lymphocytes, 4 per cent monocytes, 1 per cent basophiles, 15 per cent eosinophiles. On five other differential counts between attacks, the eosinophiles ranged from 6 to 8 per cent. No explanation for this elevation can be given. Extensive allergic studies were not possible, and there was no clinical evidence of any parasitic infestation. The urine examination was normal. The sedimentation rate during attacks was elevated to as high as 21 mm. per hour (Cutler method), but between attacks was always found to be normal. The Kahn test was negative. Examination of the prostatic fluid showed one to four pus cells per high power field. The blood uric acid was 2.8 mg. per hundred cubic centimeters; the urea-nitrogen 15 mg. per hundred cubic centimeters, the chlorides 445 mg. per cent, and the blood cholesterol 169 mg. per hundred cubic centimeters. The agglutination test for undulant fever was negative. The electrocardiogram was normal. A roentgenogram of the chest revealed no abnormalities and roentgenograms of the hands, wrists, elbows, feet, ankles and knee joints showed no evidence of pathologic changes.

Inasmuch as the attacks in this patient were not incapacitating, the patient was returned to duty with advice concerning avoidance of strenuous physical activity, since he believed such activity was a factor in the production of his symptoms, although we could not prove this as an etiologic factor.

COMMENT

This patient presents the symptoms and findings of recurrent attacks of acute swelling, redness, pain, and tenderness of various joints and their surrounding tissues which have been described by Hench and Rosenberg as characterizing palindromic rheumatism. The irregularity of the intervals between attacks, the rapid onset and subsidence of the attacks, and the complete lack of demonstrable sequelae are also characteristic of the condition. The significance of an increase in the eosinophile count in this patient is in doubt. Three patients in the series reported by Hench and Rosenberg had slight elevations of the percentages of eosinophiles between attacks, but no increases were noted during attacks.

Although the etiology of this condition and its treatment are unknown, it is believed important that it be recognized, since patients with palindromic rheumatism may be reassured that, in spite of the frequency and severity of their attacks, no joint deformities will result in contrast to the deformities often resulting from other types of articular disease.

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EDITORIAL

PSEUDOHEMOPHILIA

HEMORRHAGIC diseases present a complicated problem, and there is still much uncertainty regarding the fundamental nature and relationship of many of the cases showing such disorders. This may be attributed in part to the number and complexity of the factors involved in hemostasis and to their variability, as well as to the inadequacy, cumbersome nature and relative lack of precision of many of the laboratory procedures available for their investigation. Variations in technic in the hands of different workers have also been confusing.

It has been customary to classify cases of hemorrhagic disease into three main groups according to their pathogenesis: those with a deficiency of blood platelets, those with some disturbance of the coagulation factors of the blood, and those with a demonstrable or presumed abnormality of the walls of the minute vessels.

The first group includes the primary and secondary thrombocytopenic purpuras. This group is relatively clear cut, and most of the cases can be recognized easily by the characteristic reduction in blood platelets, prolonged bleeding time, defective clot retraction and positive tourniquet test, whereas the coagulation time is usually normal.

The second group includes hemophilia and those cases of bleeding associated with a reduction of prothrombin or of fibrinogen. These conditions also can usually be distinguished clearly by the available tests. Hemophilia is nearly the antithesis of thrombocytopenic purpura, with its prolonged coagulation time, but normal platelet count, bleeding time, negative tourniquet test and (eventually) normal clot retractility, as well as its peculiar hereditary nature.

The third group includes cases which have been termed nonthrombocytopenic purpura or anaphylactoid purpura, including the syndromes described by Schoenlein and by Henoch. Here too would be included cases of hereditary hemorrhagic telangiectasia, in which all other factors are normal and localized abnormalities in the capillaries are conspicuous and easily demonstrable. In general these cases are less well understood because of the lack of adequate methods of testing the functional integrity of the vessels.

Although most cases of hemorrhagic disease can now be fitted into well recognized groups, there have been a considerable number of "atypical" cases reported during the past 30 years. The recognition and separation of the hypoprothrombinemias is a relatively recent accomplishment. Many reports have appeared describing other groups of cases which it was thought might constitute a distinct syndrome.

One of the earliest and still frequently quoted contributions was that of

Glanzmann.[1] He reported eight families containing from two to many bleeders in several generations, in which the tendency affected and was transmitted by both sexes. The cases were characterized clinically by bleeding from the mucous membranes, from cuts and abrasions, operative wounds and after dental extractions, but without purpura and with little tendency to intracutaneous bleeding. They were characterized by a normal coagulation time, a normal (or insignificantly reduced) platelet count, and a normal bleeding time,[2] but clot retraction was defective or absent. He described morphological and functional abnormalities in the platelets which he thought were responsible for the disturbance, and termed the condition "thrombasthenia." Except for two partially confirmatory reports [3, 4] which appeared shortly after Glanzmann's article, not a single case conforming to his description has since been recorded. One must conclude either that this syndrome is excessively rare, or that Glanzmann's observations were faulty. His conception of "thrombasthenia," however, a functional deficiency of the platelets, has persisted and is still a matter of controversy.

von Willebrand (in 1926 and more fully in 1929 [5]) reported a large series of cases which resembled those of Glanzmann as far as their clinical features and familial occurrence are concerned. They occurred in three families of Swedish descent which had lived for a thousand years in isolated communities in Finland where there was considerable inbreeding and but little admixture with outside populations. He obtained records of 124 members of these families, of whom 48 gave a history of bleeding; 17 were males and 31 females, of whom 10 females died of hemorrhage. He was able to study 18 cases, of which 13 on some occasion showed the following characteristic features: a normal coagulation time, a normal or high platelet count, and normal clot retractility, but a prolonged bleeding time and in the severer cases a positive tourniquet test. The bleeding time, however, was not uniformly or invariably prolonged; it sometimes varied on different occasions in the same patient and tended approximately to parallel the severity of the symptoms.

von Willebrand attributed the bleeding principally to a functional abnormality of the platelets ("Thrombopathie"), but recognized a "vascular component." He advanced evidence—not entirely convincing—that the platelets agglutinated less readily in a capillary glass tube than did those of normal blood.

[1] GLANZMANN, E.: Hereditäre hämorrhagische Thrombasthenie. Ein Beitrag zur Pathologie der Blutplättchen, Jahrb. d. Kinderh., 1918, lxxxviii, 1–42, 113–141.

[2] Glanzmann's article has been misquoted in many journal articles and textbooks in stating that the bleeding time was prolonged. If a few cases of typical thrombocytopenic purpura, so diagnosed by Glanzmann, are disregarded, the bleeding time in all his cases is recorded as *normal*.

[3] KRÖMECKE, F.: Zur Frage der hereditären hämorrhagischen Diathese (Thrombasthenie), Deutsch. med. Wchnschr., 1922, xlviii, 1102–1105.

[4] ZANDE, F. VAN DER: Pseudohemophilia, Nederl. tijdschr. v. geneesk., 1923, lxvii, 544–553.

[5] v. WILLEBRAND, E. A., and JÜRGENS, R.: Über ein neues vererbbares Blutungsübel: Die konstitutionelle Thrombopathie, Deutsch. Arch. klin. Med., 1933, clxxv, 453–583.

Because of the much greater incidence and severity of the disease in females in his series, he thought the defect was inherited as a sex-linked dominant character. The transmission from father to son, brought out more strikingly in subsequent studies by other observers, indicates that this can not be the case, and the trait is probably inherited as a simple incomplete dominant character of ordinary type. A number of cases clinically indistinguishable have since been reported[6] without any familial history of bleeding, and the disease can not be excluded on this ground. The same is true of hemophilia.

von Willebrand's observations in the main have been confirmed by many subsequent observers. Among others, Minot[7] studied five cases in a family of 31, of whom 11 (over four generations of males) were bleeders. Clinically and hematologically they corresponded closely to von Willebrand's description. Little and Ayres[8] studied two sisters in a family of 71, of which 24 gave a history of bleeding. These two cases differed only in having splenic enlargement. One bled to death following attempted splenectomy.

Geiger and Evans[9] reported a similar case of severe gastrointestinal bleeding in a man and in two of his children in a family of nine, of whom five were bleeders. They present an excellent review of previously reported cases. Macfarlane[10] studied five such cases, and Estren, Médal and Dameshek[6] reported 11 cases which were typical except that in only five was a family history of bleeding obtained.

The hematological features of these cases have already been described. Cytologically they have been normal or showed those changes which are commonly associated with hemorrhage. Clinically they present a fairly characteristic picture which differs in some respects from both hemophilia and thrombocytopenic purpura.

Bleeding commonly starts in early life, sometimes in infancy, and is often troublesome in small children whose tumbles and minor traumata frequently result in extensive ecchymoses and persistent oozing from superficial abrasions. It may persist throughout life, but in many cases has become less troublesome after adolescence, particularly the tendency to epistaxis.

Bleeding from the mucous membranes, persistent and often profuse, is a common and highly characteristic feature. Epistaxis is very common, as well as bleeding from the gums and from the uterus. Bleeding occurs

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[9] Geiger, A., and Evans, E. G.: Atypical hereditary hemorrhagic syndromes, Internat. Clin., 1938, ii, 135–157.

[10] Macfarlane, R. G.: Critical review: The mechanism of hemostasis, Quart. Jr. Med., 1941, x, 1–29.

less frequently from the gastrointestinal tract and only occasionally from the kidneys or lungs. Persistent oozing from superficial cuts and abrasions is common and resembles that in hemophilia. Bleeding often occurs from operative incisions, is extremely troublesome and may be fatal. These patients are poor "surgical risks," and unessential operations and particularly splenectomy should be avoided. They may be even worse risks than cases of hemophilia or thrombocytopenic purpura, since transfusions (or injections of antihemophilic globulin in hemophilia) will usually stop bleeding temporarily, whereas in this disease they have relatively little or no effect upon the bleeding. Troublesome bleeding is common after dental extractions and may occur in children after loss of deciduous teeth.

Bleeding into the skin is common in the form of ecchymoses, usually following trauma, but is less conspicuous than in thrombocytopenic purpura, and typical petechiae are much less common. Bleeding into the joints has occurred in several cases, but is relatively uncommon, in contrast to hemophilia. Intracranial and retinal hemorrhages have been recorded, but are very rare.

The tendency to bleed varies markedly in different individuals and in the same individual at different times. The tendency does not necessarily parallel the length of the bleeding time or the result of the tourniquet test, although there is a general tendency to do so. Precise figures as to mortality are not available. As in hemophilia, there is a high probability of recovery from any one individual attack of bleeding, but the "accumulated" mortality is substantial. Of the 62 collected cases reported by Estren et al.[6] which had been adequately studied, only two died of hemorrhage. This is undoubtedly an underestimate of the ultimate mortality. Geiger and Evans[9] reported 17 fatalities among 97 bleeders, collected largely from previous reports. As adequate blood studies had been made in only one of these fatal cases, it is possible that in some the bleeding may have been due to some other cause. However, as other bleeders in the same families showed typical manifestations of the disease, there is a strong presumption that most of them died as a result of it. Geiger and Evans' figures may underestimate the ultimate mortality, as many of the survivors were not followed throughout their life span. All but one of the fatal cases were in women. This greater mortality is not due primarily to the additional risk from uterine bleeding, as there was a greater general tendency to bleed in most of these cases. The reason for this sex difference is not known.

The pathogenesis of the bleeding is still undetermined. Attempts to demonstrate a functional defect of the platelets have been mentioned, but the evidence is not convincing. It is probably not due to a dysfunction of the spleen. In most cases the organ has not been enlarged, or at least not palpable. In the few cases in which splenectomy has been carried out, there has been little if any effect on the bleeding. At best, it is in no way comparable with that often seen following splenectomy in thrombocytopenic purpura.

Macfarlane [10] has emphasized the importance of the rôle played by the minute vessels in hemostasis. Normally trauma to these vessels is quickly followed by a constriction which mechanically checks oozing until sufficient time has elapsed to permit agglutination of platelets and the formation of a firm clot which will occlude them. In certain pathologic states including this syndrome and thrombocytopenic purpura, these vessels appear to be abnormal, they fail to undergo constriction after injury, and permit continuous oozing which prevents the formation of an occluding clot or thrombus. He reports that the capillary loops in the nail beds in these diseases are distended and tortuous. When a single capillary loop in a normal individual is punctured with a fine glass fiber, after a slight hemorrhage it quickly contracts and disappears and remains invisible for from 20 minutes to two hours. In these diseases there was no constriction after puncture, and bleeding into the tissues persisted.

These observations of abnormal-appearing capillary loops which fail to constrict and which bleed progressively after injury have been confirmed. Perkins [11] has reported similar findings in one case, and Levy [12] in three cases of this syndrome. It seems possible, therefore, that vascular abnormalities play an important and perhaps a major rôle in the bleeding tendency, although the tourniquet test is not so uniformly and strongly positive as might be expected if this is the case. The existence of some associated defect of coagulation, possibly due to an abnormality of the platelets, has not been excluded.

Treatment has been unsatisfactory. Superficial bleeding can usually be controlled by local applications of fibrin foam and thrombin solution under moderate pressure. Internal hemorrhages, however, have been relatively uninfluenced by transfusions and other customary procedures, although they counteract the effects of acute blood loss. There are spontaneous variations in the tendency to bleed, however, and in a majority of the cases bleeding eventually ceases before exsanguination occurs.

In addition to those cases precisely conforming to this description, many others have been reported which differ in one or more of their hematological features. As Geiger and Evans [9] have pointed out, some of these more closely resemble hemophilia, others thrombocytopenic purpura, and they might be regarded as transitional stages between these two extremes. They have questioned the possibility of subdividing these cases into clear cut groups on such a basis, pointing out that notable differences may be found between two bleeders in the same family and even in the same individual on different occasions. In the past vascular abnormalities have received inadequate attention, and until these can be more accurately appraised, it is unlikely that any satisfactory classification can be worked out.

[11] PERKINS, W.: Pseudohemophilia: Case study, Blood, 1946, i, 497–503.

[12] LEVY, L. H: Non-hemophilic hereditary hemorrhagic diathesis: Report of a family of bleeders, Ann. Int. Med., in press.

The terminology of these syndromes is chaotic. Several different names, all unsatisfactory, have been applied to this group. Thrombasthenia implies an etiology which is not proved and not generally accepted. Pseudohemophilia is perhaps equally unsatisfactory, and it has also been applied to other unrelated hemorrhagic tendencies. It has been used more often than any other in the recent literature, however, and if qualified by some such term as "von Willebrand type," it should not be misleading.

Pseudohemophilia is of academic interest because primary vascular abnormalities appear to be more signficant or at least more evident than in most of the other hemorrhagic diseases. It is also of practical significance. It is evidently more common than has been appreciated, probably at least as common as hemophilia, and it is not necessarily familial or at least demonstrably so. Recognition of the tendency is particularly important in order to avoid unexpected and unnecessary risks involved in unessential operations. Cronkite and Lozner [13] have reported such a case, an otherwise healthy soldier who bled repeatedly and protractedly after a simple hemorrhoidectomy. The occurrence of previous hemorrhage in the patient and of other bleeders in the family was not discovered until after the postoperative hemorrhages began.

P. W. C.

[13] CRONKITE, E. P., and LOZNER, E. L.: Hereditary hemorrhagic thrombasthenia with severe posthemorrhoidectomy hemorrhage, U. S. Naval Med. Bull., 1944, xlii, 161–164.

REVIEWS

Pharmacology and Therapeutics. Thirteenth Edition. Originally Written by ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S. Revised by ARTHUR GROLLMAN, A.B., Ph.D., M.D., F.A.C.P., and DONALD SLAUGHTER, B.S., M.D. 868 pages; 24 × 16 cm. Lea and Febiger, Philadelphia. 1947. Price, $8.50.

This, the 13th edition of this classic pharmacology text, has been reëdited and revised by two eminently qualified authorities. The junior author has revised the section on central nervous system depressants. The remainder of the book shows the skillful hand of Dr. Grollman.

To most practitioners of medicine, Cushny's Pharmacology needs no introduction for it has long been a standard text in this field. In bringing the book up to date, the present revisers have incorporated changes introduced by the publication of the 12th revision of the U. S. Pharmacopoeia and the British Pharmacopoeia of 1932.

The introduction deals with the method of action of drugs, their chemical character, the pharmacopoeias and pharmacopoeial preparations, and biological assays. As in previous editions, the book is divided into six major parts: Part I, The Action of Inorganic Substances; Part II, Substances Which Are Characterized Chiefly by Their Local Action; Part III, Substances Characterized Chiefly by Their Action After Absorption; Part IV, Anthelmintics; Part V, Antiseptics and Disinfectants; Part VI, Vaccines and Biologicals.

The section on general anesthetics appears to be very brief and, like most current textbooks in pharmacology, provides a very elaborate discussion of the pharmacology of chloroform, while the newer general anesthetics are given but passing mention.

The volume, however, in most respects is abreast of recent developments in the field of pharmacology. For example, one finds a discussion of folic acid, para-aminobenzoic acid and vitamin K adequately presented under the section on vitamins or accessory food substances. Also, such recent discoveries as the production of experimental diabetes by the injection of alloxan are included, and in the section on analgesics, isonipecaine is discussed.

As a whole, this edition of Cushny's original work appears to be well presented and will recommend itself to the medical student, the practitioner of medicine and the teacher in the field of pharmacology.

C. J. C.

Hygiene. Fourth Edition. By FLORENCE L. MEREDITH, B.Sc., M.D. 837 pages; 24 × 16.5 cm. 1946. The Blakiston Company, Philadelphia. Price, $4.00.

This clearly and simply written textbook is probably well suited to the needs of a college course designed to introduce the student to the problem of health and hygiene. It is divided into nine sections, including parts devoted to anatomy and physiology, history of medicine, infection, hygiene of everyday life, and, finally, a very sound section on mental health.

The work is too elementary to be used by medical students, but should help the undergraduate to understand some of the problems of medical care. The practitioner may find it useful to orient patients in relation to his own work.

T. N. C.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Gastroenterology in General Practice. By LOUIS PELNER, M.D. 283 pages; 26 × 17.5 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, $7.50.

Textbook of Medical Treatment. Fourth Edition. By Various Authors. Edited by D. M. DUNLOP, M.D., F.R.C.P., L. S. DAVIDSON, M.D., F.R.C.P., and J. W. MCNEE, M.D., F.R.C.P. 923 pages; 25 × 17.5 cm. 1946. The Williams & Wilkins Company, Baltimore. Price, $8.00.

Clinical Hematology. Second Edition. By MAXWELL M. WINTROBE, M.D., Ph.D. 862 pages; 24 × 15.5 cm. 1946. Lea & Febiger, Philadelphia, Pa. Price, $11.00.

The Nature of Disease Up To Date. An Outline of a Unitary Theory. By J. E. R. MCDONAGH, F.R.C.S. Edited by MARK CLEMENT. 168 pages; 22 × 14.5 cm. 1946. William Heinemann, London. (To be obtained from Grune & Stratton, New York.) Price, 15 s.

Heparin in the Treatment of Thrombosis. Second Edition. By J. ERIK JORPES, M.D. Foreword by J. R. LEARMONTH, C.B.E., Ch.M., F.R.C.S.E. 260 pages; 22.5 × 14 cm. 1947. Oxford University Press, New York. Price, $6.50.

Parenteral Alimentation in Surgery. By ROBERT ELMAN, M.D., Assoc. Prof. Clin. Surg., Washington University School of Medicine. 284 pages; 24 ×15.5 cm. 1947. Paul B. Hoeber, Inc., New York. Price, $4.50.

Pharmacology and Therapeutics. Thirteenth Edition, Thoroughly Revised. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S. Revised by ARTHUR GROLLMAN, M.D., F.A.C.P., and DONALD SLAUGHTER, B.S., M.D. 868 pages; 24 × 16 cm. 1947. Lea & Febiger, Philadelphia. Price, $8.50.

Cardiovascular Diseases. By DAVID SCHERF, M.D., F.A.C.P., and LINN J. BOYD, M.D., F.A.C.P., Prof. Medicine, New York Medical College. 478 pages; 26 × 18.5 cm. J. B. Lippincott Company, Philadelphia. Price, $10.00.

Foreseeing and Forestalling Tuberculosis. A Symposium. By W. E. OGDEN, M.D., F.A.C.P., F.C.C.P., G. C. ANGLIN, M.B., F.A.C.P., F.C.C.P., and W. C. KRUGER, M.B., et al., Toronto, Canada. 55 pages. Reprinted from "Diseases of the Chest."

COLLEGE NEWS NOTES

Nominations for A.C.P. Elective Offices, 1947–48

In accordance with the By-laws of The American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1947–48, are herewith announced and published:

President Elect.....Walter W. Palmer, New York, N. Y.
First Vice President.....Reginald Fitz, Boston, Mass.
Second Vice President.....Francis G. Blake, New Haven, Conn.
Third Vice President.....Charles T. Stone, Galveston, Tex.

Regular elections will take place at the 1947 Annual Session at Chicago, April 28–May 2. The Business Meeting will be held Thursday afternoon, May 1, in the Grand Ballroom of the Palmer House.

The election of nominees shall be by the Fellows and Masters of the College. The above Nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations for members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-laws.

Respectfully submitted,

Ralph A. Kinsella, St. Louis, Mo.
Asa L. Lincoln, New York, N. Y.
Jonathan C. Meakins, Montreal, Can.
George F. Strong, Vancouver, Can.
James J. Waring, *Chairman*, Denver, Colo.

Committee on Nominations

Additional Life Members

Grateful acknowledgment is made of subscriptions to Life Memberships, received January 20 through February 17, 1947, from the following Fellows of the College:

Clarence L. Andrews, Atlantic City, N. J.
Theodore F. Bach, Philadelphia, Pa.
John V. Barrow, Los Angeles, Calif.
Paul J. Breslich, Minot, N. D.
Madelaine R. Brown, Boston, Mass.
Roland Cummings, Los Angeles, Calif.
Maurice A. Donovan, Schenectady, N. Y.
Thomas B. Dunn, Oakland, Calif.
Harry E. Flansburg, Lincoln, Nebr.
William W. Fox, Atlantic City, N. J.
Cleo R. Gatley, Pontiac, Mich.
James T. Gilbert, Jr., Bowling Green, Ky.
Carl A. Hartung, Chattanooga, Tenn.
Frederick K. Herpel, W. Palm Beach, Fla.
Edwin F. Hirsch, Chicago, Ill.
B. Smith Hopkins, Jr., Urbana, Ill.

Albert A. Hornor, Boston, Mass.
James E. Hunter, Seattle, Wash.
Wingate M. Johnson, Winston-Salem, N. C.
Gordon R. Kamman, St. Paul, Minn.
Joseph Kaufmann, Montreal, Can.
Donald L. Kegaries, Rapid City, S. D.
Clyde H. Kelchner, Allentown, Pa.
O. B. Kiel, Wichita Falls, Tex.
Harold I. Kinsey, Toronto, Can.
Elmer A. Kleefield, Forest Hills, N. Y.
Roy L. Leadingham, Atlanta, Ga.
Charles E. Leonard, Oklahoma City, Okla.
Robert C. Levy, Chicago, Ill.
Horace R. Livengood, Elizabeth, N. J.
William C. Menninger, Topeka, Kans.
F. D. Mohle, Houston, Tex.
P. Morales-Otero, Santurce, P. R.
Samuel A. Munford, Clifton Springs, N. Y.
Clarence W. Olsen, Beverly Hills, Calif.
Hubert M. Parker, Kansas City, Mo.
Joseph M. Perret, New Orleans, La.
Frank B. Queen, Portland, Ore.
Edward U. Reed, Los Angeles, Calif.
Rufus S. Reeves, Philadelphia, Pa.
Edward C. Reifenstein, Sr., Syracuse, N. Y.
E. Clarence Rice, Washington, D. C.
Carl O. Rinder, Chicago, Ill.
H. Milton Rogers, St. Petersburg, Fla.
Albert H. Rowe, Oakland, Calif.
Cecil L. Rudesill, Indianapolis, Ind.
Jacob Schwartz, Brooklyn, N. Y.
Kenneth K. Sherwood, Kirkland, Wash.
George T. Strodl, New York, N. Y.
Amadeo Vicente-Mastellari, Panama, R. P.
James C. Waddell, Beatrice, Nebr.
Robert P. Wallace, New York, N. Y.
Leslie R. Webb, Springfield, Mo.
Joseph Weinstein, Brooklyn, N. Y.
Otto G. Wiedman, Hartford, Conn.
F. Eugene Zemp, Columbia, S. C.

Regional Meeting Planned for Delaware, Maryland and the District of Columbia, Baltimore, April 5, 1947

At the time of this writing, Governor Wetherbee Fort has prepared, with the coöperation of Drs. Lewis B. Flinn and Wallace M. Yater, College Governors for Delaware and District of Columbia, respectively, the tentative program of a regional meeting to take place April 5. The morning session will occur in the Gordon Wilson Hall of the University of Maryland Hospital, and will be followed by lunch in the Phipps Clinic and an afternoon session in the Hurd Lecture Hall of the Johns Hopkins Hospital.

The program will include the following papers: Studies in Rh Isoimmunization, Milton S. Sacks, F.A.C.P.; Some Observations on and Treatment of Peripheral Vascular Diseases, Louis Krause, F.A.C.P.; Use of Tracer Amounts of Radioactive Iodine for the Detection of Aberrant Thyroid Tissue, Edward F. Cotter (Associate); Some Aspects of the Surgical Treatment of Heart Disease, Alfred Blalock, F.A.C.S.; Modern Treatment of Cirrhosis of the Liver, W. Halsey Barker, F.A.C.P.; Experience with Thiouracil Treatment of Hyperthyroidism, Elliott V. Newman (by invitation); Use of the Thymol Turbidity Test in the Study of Liver Disease, Richard Mirick (by invitation); Periodic Vascular Head Pain, Edmund L. Keeney, F.A.C.P.; all of Baltimore, Md. Also: Extra Pulmonary Pneumococcal Infections, Albert A. Pearre, F.A.C.P., Frederick, Md.; County Medical Problems, Page C. Jett (by invitation), Prince Frederick, Md.; Value of Special Electrocardiographic Studies in General Hospitals, James S. Taylor (MC), USA, (Associate), Washington, D. C.; Paroxysmal Supraventricular Tachycardia with Functional Auricular-Ventricular Block, Joseph M. Barker (Associate), Washington, D. C.; Aphorisms Based on the Observation of 1037 Treated Cases of Peptic Ulcer, Lewis Gunther (MC), USN, (Associate), Bethesda, Md.; Preliminary Report on the Result of Smallpox Vaccination in 50,000 Industrial Workers, Lemuel C. McGee, F.A.C.P., Wilmington, Del.

In its work, the local committee on arrangements is receiving the valued coöperation of Dr. E. L. Crosby, Jr., Superintendent of the Johns Hopkins Hospital; of Dr. Abner McG. Harvey, Professor of Medicine in the Johns Hopkins University; and of Dr. Maurice C. Pincoffs, F.A.C.P., Professor of Medicine in the University of Maryland. The printed program will be distributed to all Fellows and Associates in this area.

Specialty Board Examinations

American Board of Dermatology and Syphilology; George M. Lewis, M.D., Secretary–Treasurer, 66 E. 66th St., New York 21, N. Y. Applications closed February 17. Written examinations, March 24, 1947; oral examinations, April 25–27, New York, N. Y.

American Board of Internal Medicine; William A. Werrell, M.D., Assistant Secretary–Treasurer, 1 W. Main St., Madison 3, Wis. Written examinations, March 17, 1947; October 20, 1947 (closing date, June 1). Oral examinations, April 24–26, 1947, Chicago, Ill. (closing date, March 15); June 5–7, 1947, Philadelphia, Pa. (closing date, April 1).

American Board of Pathology; Robert A. Moore, M.D., Secretary, Euclid Ave. and Kingshighway, St. Louis 10, Mo. Examination, June 3–4, 1947, Philadelphia, Pa. (closing date, April 15).

American Board of Pediatrics; Lee F. Hill, M.D., Secretary–Treasurer, 1818 12th St., Des Moines, Iowa. Examinations, April 25–27, 1947, The Palmer House, Chicago, Ill.; May 10–11, 1947, The Children's Hospital, Buffalo, N. Y.

American Board of Psychiatry and Neurology; F. J. Braceland, M.D., Secretary-Treasurer, 102–10 2nd Ave., S.W., Rochester, Minn. Examinations (tentative dates), May 15–17, 1947, Philadelphia, Pa.

American Board of Radiology; B. R. Kirklin, M.D., Secretary-Treasurer, 102-10 2nd Ave., S.W., Rochester, Minn. Examinations, June 4–8, 1947, Atlantic City, N. J.

The American Trudeau Society, coöperating with the University of Colorado Medical School, will offer a Postgraduate Course in Thoracic Diseases, July 28

to August 9, 1947, in Denver, Colo. Fee for the course will be $100.00. Inquiries should be addressed to Cameron St. C. Guild, M.D., Executive Secretary of this Society, 1790 Broadway 19, N. Y.

The 4th International Cancer Research Conference will be held September 2 to 7, 1947 in St. Louis, Mo. The 75th Annual Meeting of the American Public Health Association will take place October 6 to 10, 1947 at Atlantic City, N. J.

The 11th Annual Postgraduate Institute of the Philadelphia County Medical Society will be held at the Bellevue-Stratford Hotel, April 15 to 18, 1947. The theme will be "Symposia on Medical Progress." Subjects discussed will include thyroid problems, diabetes, vitamins and hormones, intestinal disorders, kidney pathology, peripheral vascular diseases, antibiotics, hypertension, diseases of the lung, neuropsychiatry, stomach and duodenum, allergy, skin disorders, and otolaryngological diseases. Two evening meetings at the Society Building will concern childhood and infancy disorders, and obstetrical and gynecological problems. There will be technical and scientific exhibits.

The registration fee for non-members is $5.00 for the course. Out-of-town physicians planning to attend are urged to make their hotel reservations immediately. Further information may be had from Gilson C. Engel, M.D., Director, 301 South 21st St., Philadelphia 3, Pa.

The third annual convention of the American Society for the Study of Sterility will be held at the Hotel Strand, Atlantic City, New Jersey, on June 7 and 8, 1947, preceding the annual A.M.A. Convention. The general theme of the meetings will be that of attempting to disseminate to the physician treating marital infertility an overall picture of the latest advances in reproduction. The convention will include original papers, round table discussions, scientific exhibits, and personal demonstrations. Registration for the sessions is open to members of the medical and allied professions.

Additional information may be obtained from the secretary, Dr. John O. Haman, 490 Post Street, San Francisco, Calif.

Reports on Recent Regional Meetings

I. New England—January 28, 1947

Held at Hanover, N. H., this meeting was reported as a very successful one. The fine program was printed in the February News Notes. Attendance was as follows: Connecticut, 10; Massachusetts, 31; Maine, 9; New Hampshire, 57; New York, 1; Rhode Island, 8; Vermont, 12.

II. Lansing, Michigan—January 29, 1947

A Regional Meeting of the College was held at Lansing during the afternoon and evening of January 29th. A severe blizzard on that date interfered with the attendance; there were 35 members present, according to the report by Dr. William M. LeFevre, F.A.C.P., Muskegon, Secretary. Arrangements were made by Dr. Milton Shaw, F.A.C.P., Lansing; and Dr. Leo G. Christian, F.A.C.P., Lansing, acted as chairman of the meeting. The program consisted in the following papers: Non-

surgical Treatment of Lung Abscess, Christopher Stringer, F.A.C.P.; Simulation of Angina Pectoris by Diaphragmatic Hernia, Joseph Rozan (by invitation); Salmonellosis and Shigellosis, H. E. Cope (by invitation); Blood Derivatives, A. B. Mitchell (by invitation); Rh Factor, G. D. Cummings (by invitation).

III. Eastern Pennsylvania—February 7, 1947

The Ninth Annual Regional Meeting of The College for Eastern Pennsylvania was held at Philadelphia on February 7. The States of Delaware and New Jersey were invited to join in and a good representation of the members was present. There were also in attendance those who were taking The College postgraduate course in Growth, Isotopes, and Tumor Formation. In fact, the morning program of the postgraduate course was open also for all those in attendance at the Regional Meeting.

Papers on the formal program were of uniformly excellent quality. A midday luncheon was held at The College Headquarters with a hundred and ninety-five in attendance and a dinner meeting was held at the Warwick Hotel with an attendance of two hundred and fifty. In all, more than 300 members from the area participated in some part of the Meeting. Chief speakers at the evening dinner meeting were Dr. Alexander M. Burgess, College Governor for Rhode Island and Member of the American Board of Internal Medicine, and Mr. E. R. Loveland, Executive Secretary of The College.

IV. Birmingham, Alabama—February 8, 1947

The State of Alabama, under the Governorship of Dr. E. Dice Lineberry, held its first formal Regional Meeting for that state at Birmingham, February 8, 1947. There was a gratifyingly fine attendance with practically all the members of The College present from Alabama, some visitors from adjoining states and a considerable number of guests.

The afternoon program included the following papers: Primary Splenic Hematopenia, William H. Riser, Jr. (by invitation); Recent Studies on the Chemotherapy of Leukemia, Howard E. Skipper, Ph.D. (by invitation); Anticoagulants in Acute Myocardial Infarction, Oliver Welch (Associate); The University of Alabama Medical College, Roy D. Kracke, Dean (by invitation); Clinical-Pathological Conference, James S. McLester, F.A.C.P., and Roger D. Baker (by invitation).

Dr. Hugh J. Morgan, President-Elect of The College, Nashville, Tenn., was the chief speaker at the dinner.

Following the Meeting, an Executive Session was held and resolutions were adopted providing that Alabama shall hold a regular Annual Regional Meeting under the direction of its Governor. Dr. Olney Russell, F.A.C.P., was elected Secretary-Treasurer for future meetings of this character.

Total attendance exceeded one hundred.

V. Wichita, Kansas—March 21, 1947

Annual meetings for members of the College residing in Kansas have been resumed. The program of this first post-war meeting, arranged by College Governor Harold H. Jones, Winfield, included a morning Clinical-Pathological Conference, conducted at the St.Francis Hospital by Christian A. Hellwig, M.D. (by invitation); luncheon at the Allis Hotel; and an afternoon session devoted to the following topics: Causes and Treatment of Edema, George F. Corrigan, F.A.C.P., Wichita; Cytochrome C, Samuel Zelman (by invitation), Topeka; Electrocardiogram in Angina Pectoris, Fred J. McEwen, F.A.C.P., Wichita; Medical Advances in Relation to Colloidal Chemistry, Clarence W. Erickson, F.A.C.P., Pittsburg; Hypoglycemia in

the Fatigue Syndrome, Lee H. Leger, F.A.C.P., Kansas City; Protein Metabolism, George A. Westfall, F.A.C.P., Halstead; Some Aspects of Choline Metabolism, Frederic W. Hall (Associate), Winfield.

Dr. Paullin Awarded Medal for Merit

Dr. James E. Paullin, Atlanta, Ga., Regent and former President of the College, received the President's Medal for Merit on January 31, 1947, at the hands of Secretary of the Navy Forrestal. The citation read as follows:

"Dr. James Edgar Paullin, for exceptionally meritorious conduct in the performance of outstanding services to the United States since 1943. Dr. Paullin served as Honorary Consultant to the Bureau of Medicine and Surgery of the Navy Department while also serving as a member of the Directing Board of the Procurement and Assignment Service of the War Manpower Commission during a period when the solution of problems of vital importance to the successful conclusion of the war required the intensive and unremitting efforts of all concerned. By his self-sacrifice and the employment of his high professional prestige, his talents as a physician and surgeon, and his abilities for successful organization of professional groups, he rendered the most responsible, notable and distinguished service. To the Navy directly, through his contributions as Honorary Consultant, and to all of the Armed Services through his achievements with the War Manpower Commission, Dr. Paullin's advice and direction were of exceptional and invaluable aid and assistance."

Major Bain L. Heffner (Associate), Greensboro, N. C., was awarded the Army Commendation Ribbon on August 26, 1946, by Major General Ray E. Porter, in recognition of his "exceptionally meritorious conduct in the performance of outstanding services as Commanding Officer of the 368th Station Hospital, Fort Gulick, Panama Canal Zone."

Dr. J. C. Geiger, F.A.C.P., San Francisco, Calif., has been honored by the award of the Grand Ducal Order of the Oak Crown of the House of Nassau of the Grand Duchy of Luxembourg, in the Grade of Officer, first class. The decoration was accompanied by the citation, "For distinguished services to the Duchy of Luxembourg and its citizens and as a great humanitarian in the field of public health."

Dr. Francis R. Dieuaide, F.A.C.P., New York, N. Y., formerly Lieutenant Colonel, (MC), AUS, is the recipient of the Legion of Merit, awarded for his splendid record as Chief of the Tropical Disease Treatment Branch of the Surgeon General's Office, February, 1943, to September, 1945.

The Legion of Merit has been awarded to Dr. John A. Layne, F.A.C.P., Great Falls, Mont., formerly Major, (MC), AUS. Dr. Layne's outstanding professional and administrative skill in organizing and conducting the Medical Section of the Gardiner General Hospital, September, 1944, to April, 1946, is cited.

Colonel James B. Anderson, (MC), USA, F.A.C.P., Bradenton, Fla., has been awarded the Legion of Merit for outstanding services, unusual clinical ability and administrative skill, demonstrated in his activities as commanding officer, Ashburn General Hospital, February, 1943, to October, 1945.

Col. Raymond O. Dart, (MC), USA, F.A.C.P., has succeeded Col. James E. Ash, (MC), USA, F.A.C.P., as Director of the Army Institute of Pathology, Washington, D. C.

Col. Arden Freer, F.A.C.P., has retired from the Medical Corps, U. S. Army, in which he held the position of Chief of Medical Consultants Division in the Surgeon General's office. Dr. Freer served in the Army for 32 years. He is now a member of Dr. Hawley's staff in the Veterans Administration. Col. Henry C. Dooling, (MC), USA, F.A.C.P., formerly Chief Health officer, the Panama Canal, has been appointed to succeed Col. Freer.

Brigadier General Charles C. Hillman, (MC), USA, F.A.C.P., has retired from the service to become Director of the Jackson Memorial Hospital, Miami, Fla.

Dr. Edward L. Turner, Dean of the new University of Washington School of Medicine, in Seattle, has announced the appointment of the following as Clinical Professors of Medicine: Edwin G. Bannick, F.A.C.P.; Lester J. Palmer, F.A.C.P.; Charles E. Watts, F.A.C.P. Dr. Roscoe L. Pullen, F.A.C.P., has been appointed Associate Professor of Medicine and Director of Hospital Planning.

Dr. Victor E. Johnson, F.A.C.P., Chicago, Ill., Secretary of the Council on Medical Education and Hospitals of the American Medical Association, and Professorial Lecturer in Physiology at the University of Chicago, has accepted appointment, beginning in April, as Professor of Physiology in the Mayo Foundation for Medical Education and Research, Rochester, Minn. In October, 1947, Dr. Johnson will succeed Dr. Donald Balfour as Director of the Foundation.

Dr. James J. Short, F.A.C.P., Los Angeles, Calif., formerly Associate Clinical Professor of Medicine in the New York Postgraduate Medical School, has been appointed Associate Professor of Medicine and Director of the Department of Internal Medicine in the Graduate School of the College of Medical Evangelists.

Dr. Ralph L. Shanno, F.A.C.P., Forty Fort, Pa., has been elected President of the Mercy Hospital Staff (Wilkes-Barre) for 1947.

Dr. D. Ward Scanlan, F.A.C.P., was recently elected Medical Director of the Atlantic City Hospital, Atlantic City, N. J.

Dr. David Scherf, F.A.C.P., New York, N. Y., has been made an honorary member of the Brazilian Society of Cardiology and a corresponding member of the Argentine Medical Society.

Dr. Albert S. Hyman, F.A.C.P., New York, N. Y., has been appointed Consulting Cardiologist to the Veterans Administration Hospital, Castle Point, N. Y. Following four years of service in the Navy Medical Reserve Corps, Dr. Hyman has prepared for publication a book, "Psychosomatic Heart Disease," based largely on experiences in the combat area.

Officers of the Institute of Medicine of Chicago, elected for the year 1947, include the following Fellows of the College: Dr. William H. Welker, Vice President, Dr. George H. Coleman, Secretary, and Dr. Grant H. Laing, Treasurer. Dr. LeRoy H. Sloan and Dr. J. Roscoe Miller were elected Governors of the Institute.

Dr. Aaron E. Margulis, F.A.C.P., has been appointed Professor of Bacteriology, Executive Officer of the Department of Bacteriology, and Director of the Hospital and Dispensary Services of Bacteriology in the New York Post-Graduate Medical School and Hospital, following the death of Ward J. MacNeal. At the time of Dr. Margulis's appointment, he held an Assistant Professorship in Pathology in this institution.

Dr. Frank B. Queen, F.A.C.P., Denver, has been appointed Professor of Pathology at the University of Oregon Medical School, Portland, and director of the state cancer control program, effective September 20. Dr. Queen, who graduated at Washington University School of Medicine, St. Louis, in 1929, has served on the faculties of the universities of Rochester, Pennsylvania, Colorado and Northwestern.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to February 13, 1947 inclusive).

Malcolm L. Barnes, Louisville, Ky. (Lt. Col., MC, AUS)
Benjamin B. Blum, Petoskey, Mich. (Capt., MC, AUS)
Norman Q. Brill, New York, N. Y. (Lt. Col., MC, AUS)
George W. Burnett, Oil City, Pa. (Major, MC, AUS)
Leroy E. Burney, Indianapolis, Ind., (Col., USPHS)
Walter P. Davenport, Appleton, Minn. (Col., MC, USA)
Abraham M. Gordon, Louisville, Ky. (Capt., MC, AUS)
Bain L. Heffner, Greensboro, N. C. (Major, MC, AUS)
Russell W. Kerr, Kansas City, Mo. (Major, MC, AUS)
Thomas H. Pargen, Baton Rouge, La. (Comdr., MC, USNR)
Seymour C. Schwartz, Syracuse, N. Y. (Col., MC, USA)
William L. Sheep, Washington, D. C. (Brig. Gen., MC, USA)
Edward T. B. Weidner, Philadelphia, Pa. (Col., MC, USA)

OBITUARIES

DR. PAUL PRESSLY McCAIN

The medical profession and the whole State of North Carolina were deeply shocked and grieved over the untimely death of Dr. Paul Pressly McCain in an automobile accident near Raleigh, N. C. on November 25, 1946. Dr. McCain was traveling to Raleigh for a Committee meeting of the North Carolina Medical Society.

Paul Pressly McCain, A.B., M.D., LL.D., F.A.C.P., Sanatorium, N.C. Born, Due West, S. C., June 26, 1884; attended Erskine College and the Atlanta College of Physicians and Surgeons; M.D., 1911, University of Maryland School of Medicine; became affiliated with the North Carolina Sanatorium in 1914 as Chief of Medical Service and Assistant Superintendent and became Superintendent and Medical Director in 1924, an appointment he held to the time of his death; Assistant Professor of Medicine, Duke University School of Medicine, Durham; Diplomate, American Board of Internal Medicine; formerly served as President of his County Medical Society, his State Medical Society, the Southern Tuberculosis Conference, Southern Sanatorium Association, National Tuberculosis Association, and as Director and Member of the Executive Committee of the North Carolina Tuberculosis Association; Member, American Trudeau Society, American Clinical and Climatological Association and the Southern Medical Association; Member of the Sub-committee on Tuberculosis of the National Research Council; was also Superintendent, Medical Director and Director of the Extension Department of the North Carolina Sanatorium for the Treatment of Tuberculosis; Superintendent, Western North Carolina Sanatorium, Black Mountain; Member of the Editorial Board of the *North Carolina Medical Journal;* Trustee, Flora Macdonald College, Red Springs; Fellow of The American College of Physicians since 1924.

It can be said without fear of contradiction that Dr. McCain was the most beloved, the most respected and the most useful physician in North Carolina. His work in the field of tuberculosis was known throughout the world. He combined the science and the art of medicine in the truest sense of the word. His advice and counsel were sought by hosts of people, both within and without the profession. His warm spirit, his deep understanding and his genuine love of his fellowman were expended without stint and he will be deeply mourned and sorely missed by people in all walks of life. Dr. McCain was a credit to his family, his friends, his profession, and his life was a potent influence for good in the affairs of The American College of Physicians. The members of the College in North Carolina deeply mourn his passing and extend the hope that time and a beneficent Providence will eventually afford to his family a measure of comfort.

PAUL F. WHITAKER, M.D., F.A.C.P.,
Governor for North Carolina

DR. SAMUEL BARBASH

Samuel Barbash, M.D., F.A.C.P., died suddenly of myocardial infarction on November 14, 1946, at his home, 1902 Pacific Avenue, Atlantic City.

Dr. Barbash was born in Tarnapol, Austria, January 29, 1884, and was brought to this country when nine months old. He attended the Philadelphia Public Schools and received his medical education at the Medico-Chirurgical College of Philadelphia. Upon receiving his degree of M.D. in 1905, he began his medical career by becoming the second interne ever appointed by the Atlantic City Hospital. Thereafter he served the Hospital well and truly until the time of his death, first as Chief of Dispensaries from 1906 to 1911, then as Chief of Medicine from 1912, and as both active Chief and Medical Director from 1935. He saw the Hospital grow from a small cottage of sixteen beds to a three hundred bed, Class A institution. Few contributed as much, none contributed more, to its growth and attainments.

He served as Resident Medical Director of the Jewish Seaside Home for Invalids, and was Consultant in Medicine and Physiotherapeutist, at the Betty Bacharach Home for Afflicted Children in Longport. He was a Past President of the Medical Society of Atlantic County, and of the Board of Medical Examiners of New Jersey, of which he had been a member since 1939. He was a Diplomate of the American Board of Internal Medicine; member of the Medical Society of the State of New Jersey, Medical Club of Philadelphia, American Medical Association, American Heart Association, and American Association of the History of Medicine. He had been a Fellow of the American College of Physicians since 1929.

He took an active interest in his community and its civic problems; he was a member of the Chamber of Commerce, the Kiwanis Club, and a Mason.

Dr. Barbash was a superior clinician, an able administrator, a constructive citizen and a loyal friend. His counsel was in constant demand by all, but especially by his juniors, and his helping hand contributed much to the professional advancement of more than a few. Much of his ebbing energy was spent in assuring a continued vitality to the Staff of the institution he loved so well, the Atlantic City Hospital, by husbanding and channeling the resources of the returning veterans. Fully aware of his limited cardiac reserves, he curtailed his private practice for months, but continued to give his energy unstintingly to the Hospital as Medical Director and to the State Board of Medical Examiners.

His enthusiasm was contagious. His energy was boundless. His kindly leadership was vigorous and unrelenting. His accomplishments were unsurpassed. His passing has left a rent in the community fabric. Dr. Barbash's impact upon the profession will be felt for years.

HILTON S. READ, M.D., F.A.C.P.

COLONEL FRANK W. WILSON

Colonel Frank Wiley Wilson, M.C., U.S.A., died on April 20, 1946, of a heart ailment at the Moore General Hospital at Swannanoa near Asheville, North Carolina, of which hospital he was the commanding officer.

Colonel Wilson was born on April 29, 1888, at Greenville, North Carolina. He obtained his medical degree from the University of Maryland in 1914. He was given a reserve commission in the medical service of the Army in August 1915 and, after graduation from the Army Medical School in 1916, he was appointed to the Medical Corps. His first service was on the Mexican border, followed by oversea duty in World War I. Since that time he had three tours of duty at Walter Reed Hospital in Washington and a long period of service at Fort Benning, Georgia. In 1934 he completed the advance course at the Medical Field Service School at Carlisle Barracks. He was placed in charge of the Station Hospital at Camp Shelby, Mississippi, in 1940 and in 1942, when the Moore General Hospital was established, he was assigned to its command and awarded the Legion of Merit in February 1946 for his services at this hospital.

Colonel Wilson became an Associate of the American College of Physicians in 1936, and a Fellow in 1939. He was also a Fellow of the American Medical Association and a member of the Georgia State Medical Society. He was a Diplomate of the American Board of Internal Medicine.

Colonel Wilson is survived by his widow, Mrs. Mary Inez Wilson, and five brothers, among them Major General Durward S. Wilson, retired, Colonel Carl B. Wilson of the Infantry and Colonel Bascom L. Wilson, Medical Corps.

Major General NORMAN T. KIRK, M.D., F.A.C.P.,
Governor for the Medical Corps, U. S. Army

DR. PARLEY NELSON

Dr. Parley Nelson (Associate) of Rexburg, Idaho, died September 12, 1946, following a stroke; age, 71 years.

Dr. Nelson was born February 17, 1875; he attended Jefferson Medical College of Philadelphia, receiving his medical degree in 1908.

He was formerly City Physician to Manti, Utah, and County Physician at Sanpete, Utah. He served as internist at the Spencer Clinic at Idaho Falls for some years. He had also been City Physician at Rexburg, Utah. For a number of years he had been a member of the Idaho State Board of Medical Examiners.

He became an Associate of The American College of Physicians in 1926.

CHICAGO: CENTER OF MEDICAL EDUCATION, RESEARCH AND PRACTICE

MEMBERS of the American College of Physicians who attend the Twenty-eighth Annual Session will find Chicago a center of vital activity in the ever-widening fields of medical education, research and practice. By virtue of its fine tradition and heritage, this city, situated on the plains of the Great Lakes, may well become the medical capital of the world.

The Palmer House, General Headquarters
Twenty-Eighth Annual Session

Chicago is the site of four class A medical schools, one of them first and another third in enrollment among sixty-nine medical schools last year. It is the only city in the world with three internationally known dental schools. This city is the home of a dozen national and international organizations active in medicine and related fields, the site of the world's largest general

charity hospital, the center of medical publishing and medical libraries, a pioneer in atomic medicine, and the home of the world's largest medical society.

Among these organizations are the American Medical Association, the American College of Surgeons, the American Association of Industrial Physicians and Surgeons, the American Dental Association, the American College of Chest Physicians, the American College of Radiology, the American Congress of Physical Therapists, the Association of American Medical Schools, the American Association of Allergists, the American College of Hospital Administrators, the American Hospital Association, the American College of Nurse Anesthetists, and the American Association of Medical Record Librarians. The American Medical Association has 128,000 members; its nine-story building houses some 600 employees; and on its own presses each week some 45,000 tons of paper become journals, books, charts, pamphlets and posters which circle the globe.

The American Medical Association

Chicago's own medical society, with 7,000 members, is the largest city medical group in the world. The medical schools of the University of Chicago, the University of Illinois, Loyola University, and Northwestern University have graduated 10,616 physicians between the years of 1928 and 1946.

While it is not possible to list here all of the seventy-six hospitals of the Chicago area, it is impossible to omit mention of one of the greatest of civilian hospitals ministering to the needs of Chicago's increasing population, manned by teachers from the medical schools, all serving without pay—Cook County Hospital. Here is afforded a wealth of clinical material, and here many of the outstanding physicians of the country served their internships. Here also, in days gone by, the Illinois Training School for Nurses trained and sent into service thousands of women, many of them to high executive and teaching positions in the hospital and nursing world, a work now taken over by the Cook County School of Nursing.

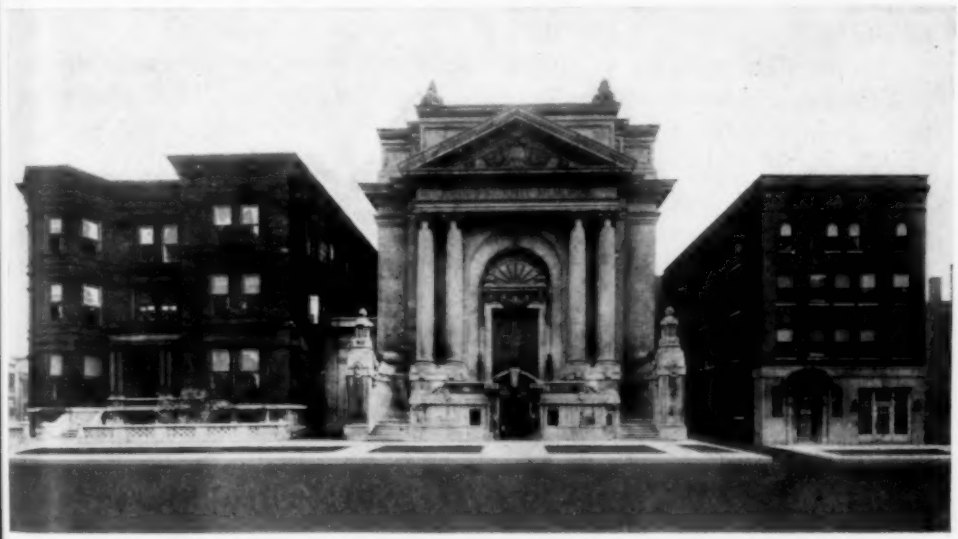
Cook County Hospital

Chicago, which has more general libraries than any other city in the world, also ranks high in its medical libraries; Billings Library at the University of Chicago, the Archibald Church Library at Northwestern University, those at Loyola University and University of Illinois, and the Crerar Library accessible to all in Chicago's loop. All of the major hospitals have libraries for the quick reference of their staff members.

Rush Medical College began instruction in two rented rooms in December, 1843. It had been chartered by the General Assembly of the State of Illinois in February, 1837. Rush Medical College held the first charter for

an institution of learning granted by the legislature of the State of Illinois; this was the oldest charter under which any school of any kind was in operation in Illinois. In the year this charter was granted, Chicago was an active, vigorous community of 3,000 people.

Daniel Brainard had journeyed to Chicago from New York State where he had spent two years with a preceptor in Whitesboro, New York. He had then studied for a year at the medical college in Fairfield, New York, and spent 1834 at Jefferson Medical College. Thus, Rush Medical College was in a way intimately linked with the home city of Benjamin Rush, signer of the Declaration of Independence, Professor of the Theory and Practice of Medicine at the University of Pennsylvania.



American College of Surgeons group, showing main building (left); John B. Murphy Memorial (center); and Surgery, Gynecology, and Obstetrics building (right)

In 1843, to obtain the degree of Doctor of Medicine it was necessary for one to have had three years of study with a so-called "respectable" physician and two courses of lectures at Rush. The regular fees amounted at that time to sixty-five dollars and the graduating fee was twenty dollars. Austin Flint lectured to the students during the second course of lectures. In 1849 Dr. Nathan Smith Davis came from New York City to teach physiology and pathology at Rush. Dr. Davis was later to be known as the "Father" of the American Medical Association and its founder. Ten years later, as a result of certain changes in policy, Dr. Davis left Rush to become one of the founders and the first Dean of the Medical Department of Lind University, later known as the Chicago Medical College and still later as Northwestern University. The original Lind Block on the northwest corner of Randolph

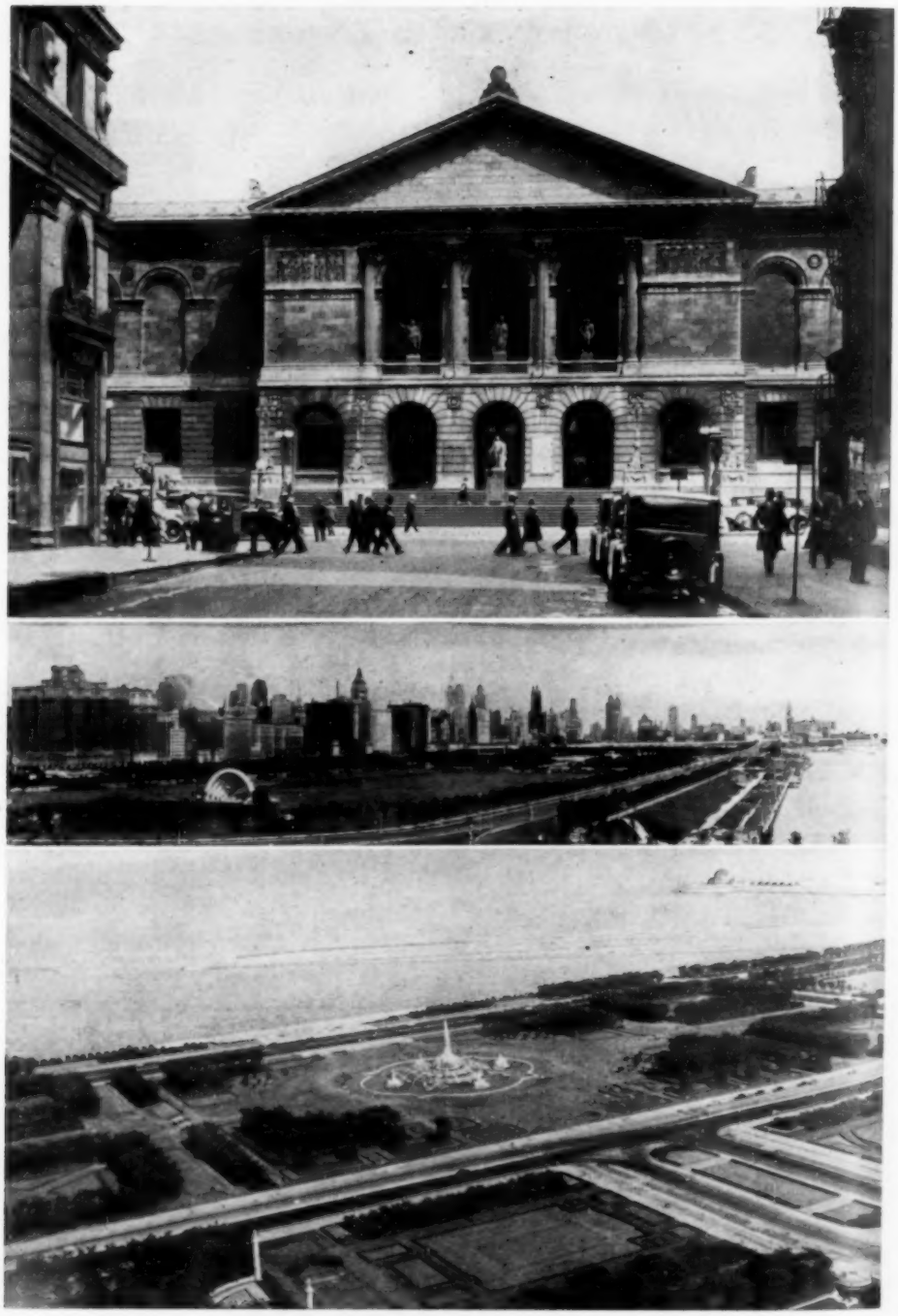
Street and Wacker Drive is still standing. From 1898 to 1941, Rush Medical College was affiliated with the progressive young University of Chicago; guided by vigorous William Rainey Harper and, in later years, by the challenging Robert M. Hutchins, this school was destined to take a leading position in the advancement of education. Until it closed its doors as an independent institution and became affiliated with the University of Illinois in 1943, Rush was always in the vanguard of progressive medical instruction and reflected the personalities of many great men of medicine: Billings, Senn, Haines, Bevan, Sippy, Herrick, and many others. Meanwhile, the University of Chicago's Medical School developed its philosophy and resources until today, provided with ample facilities for teaching and investigation, it stands as the only medical school with an entirely full-time faculty.

In 1876 Dr. Charles W. Earle formulated plans for the establishment of a College of Medicine adjacent to the Cook County Hospital. Five years later arrangements were made to bring these plans to fruition and on September 26, 1882, the regular sessions of this college began with 100 students. Ten years later a well equipped laboratory building was added to the college property. It is reported that this laboratory structure was the first of its kind in Chicago, and the first one erected by a private medical institution in the United States. In 1896 the Governor of the State of Illinois, John P. Altgeld, entered into discussion with the famous Dean of this school, Dr. William Quine, with a view to affiliation; and, on April 21, 1897, the property was leased to the University of Illinois for four years. On May 1, 1900, the College became officially designated as the College of Medicine of the University of Illinois. Since then the University has grown by leaps and bounds until today it occupies blocks of ground, with large buildings for the care of patients with medical, surgical, neuropsychiatric and special diseases. It is now about to begin a huge program of expansion.

It has been said that Northwestern University was the first medical school in the United States to apply the principles of scientific pedagogy to the teaching of medicine and surgery, and the first school to have a graded course of study. This school was founded as the result of the application of Lind University for affiliation with a medical school. Dr. Hosmer Johnson, Dr. Edmund Andrews, Dr. Ralph Isham, and Dr. Rutter received the full approval of those in control of Lind University to apply the progressive reforms and suggestions for medical education proposed and vigorously supported by Dr. Davis, and in turn invited Dr. Davis and Dr. William H. Byford from the Rush faculty to join in founding a medical department for Lind. On October 9, 1859, the first annual college term began. In his introductory remarks, Dr. Davis made the point, "that the establish-

GROUP I. (Chicago Hospitals)

Top left, Wesley Memorial Hospital — Top right, St. Luke's Hospital
Center, Northwestern University Medical School and Passavant Memorial Hospital
Bottom left, Albert Merritt Billings Hospital — Bottom right, Chicago Lying-In Hospital



GROUP II. (Chicago Views)

Top, The Art Institute of Chicago
Center, Chicago sky-line, looking north along Grant Park
Bottom, Buckingham Fountain (center); Lincoln Monument (left foreground); Adler Planetarium (right background)

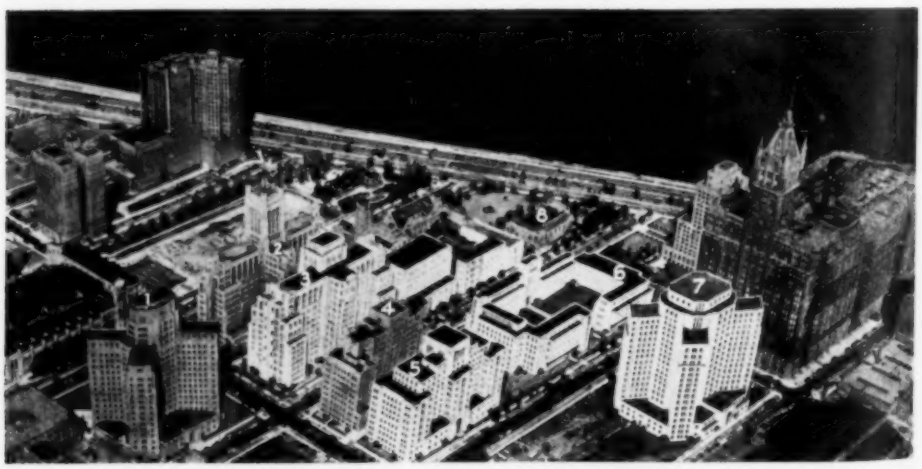
ment of this institution was partly as a result of a sincere desire on the part of the faculty to put into practical operation a system of medical college instruction more in accordance with sound educational principles and better adapted to the present state of science and art of medicine than that which has been so long adhered to by the medical schools of the country." As a result of the inevitable financial changes coming in the wake of war, Lind University released its medical faculty and they in turn opened the Chicago Medical College in October, 1863. Six years later the Chicago Medical College became affiliated with the medical department of Northwestern University.

So much for the past and the present. Plans of giant medical installations, some of them far beyond the blue-print stage, indicate an even greater focussing of medical education and research in the future. A vast monument to healing will be erected in the area bounded by Congress Street, Roosevelt Road, and Ashland and Oakley Boulevards. New buildings planned for this site by the University of Illinois include a general hospital, nursing home, library, museum and dormitories; by the State Department of Public Welfare, hospitals for the aged and chronically ill, maternity cases and mental patients; a 1,000-bed hospital by the Veterans Administration; and a $5,000,000 medical-dental building by Loyola University. These, plus the thirteen existing institutions which include the new Illinois Neuropsychiatric Institute, the Bacteriological Laboratories of the State Department of Public Health, the Illinois Research and Educational Hospitals, and the Presbyterian Hospital, will constitute a medical center equipped to deal with every phase of medical education and research. "The three-fold goal of this undertaking," said Medical Center Commission officials, "is to preserve and restore health, to seek the cause and cure of disease, and to educate those who would serve humanity."

Chicago's four medical schools, in addition to the classical courses of medical instruction, are pioneering in different phases of medical research. The University of Chicago, less than two months after the atomic bomb was dropped on Hiroshima, projected an Institute of Radiobiology and Biophysics to study the use of radioactive substances in the treatment of disease. There, through the use of isotopes, investigators will be able to study the life processes of plants and animals with minute accuracy. To house its Radiobiologic Institute, as well as allied institutes of nuclear and metal studies, the University will build a $5,000,000 set of buildings on the campus. The Goldblatt Cancer Hospital will also be added to this University's campus. The University of Illinois' activities are built around their large Research and Educational Hospitals, the Neuropsychiatric Institute for the study of nervous and mental diseases, the Institute of Juvenile Research

—first child study clinic of its kind—plus the extensive facilities of Cook County Hospital. Planned to supplement its work are a $4,000,000 addition to its hospital, a building devoted to aviation medicine, and a cancer clinic, equipped with the powerful new betatron developed in its downstate campus at Urbana.

Loyola University has trained one of every four practicing physicians in the city of Chicago. Together with her sister medical schools, Loyola is planning increased facilities for the future. A modernistic $5,000,000 building will enable the school to train 400 medical and 400 dental students at the same time. The expansion program of Northwestern University will require the spending of from $95,000,000 to $150,000,000 within the next two decades. In addition to their present medical building, and adjacent Wesley and Passavant Memorial Hospitals, there are proposed a neuropsychiatric clinic, a school of nursing, a urological institute, a children's hospital, a university clinic, and an addition to the general hospital. Some of these buildings will be completed when the University celebrates its 100th Anniversary in 1951. Adjacent to this development of Northwestern University will be the new Mercy Hospital. Mercy—the oldest hospital in Illinois—treated Civil War casualties under its original name of Illinois General Hospital of the Lakes. Plans call for a twenty-two story hospital with a 500 bed capacity, together with nurses' home, chapel, auditorium and convent; estimates of the total cost are about $10,000,000.



Northwestern University Medical Center
(Showing existing and proposed buildings)

1. Wesley Memorial Hospital
2. Ward Building (medical and dental schools)
3. Proposed institute for medical research
4. Passavant Memorial Hospital
5. Proposed new hospital
6. Proposed cancer and associated clinics
7. Veterans Administration Hospital (to be constructed)
8. Thorne Hall

Unique in hospital planning, Michael Reese Hospital, in coöperation with neighboring industries, labor groups, religious and social agencies, has set up the South Side Planning Board which will undertake the redevelopment of the area contained in the rectangle within Twelfth Street, the Pennsylvania Railroad tracks, Forty-seventh Street and Lake Michigan. This area will be completely redeveloped, and about the present hospital building will be a "campus," comprising a number of structures, including a 200 bed private and semi-private pavilion, the nucleus of a new hospital, a psychiatric and psychosomatic institute with extensive laboratories, and a convalescent hospital.

The medical exhibits in the Museum of Science and Industry, located in Jackson Park, represent a coöperative enterprise between the medical schools, medical associations, dental, pharmaceutical and hospital groups. They portray in graphic visual fashion the fundamental structure, function and derangements of the human body. Since the close of the Century of Progress in 1934, these exhibits have served an extremely valuable function in health education, especially in the public and parochial schools of Chicago and neighboring cities. Annual visits to the number of 1,250,000, including 400,000 school children on especially assigned field trips, indicate the tremendous value of these exhibits in the study of health. Various medical associations of Chicago and the State of Illinois have sponsored health lectures in the museum's main theater, and these are well attended. During the war special educational field trips of students from Fort Sheridan and the Great Lakes Naval Training Station aided in the education of men in the armed forces of this country and Canada.

Other institutions, although not connected with the four medical schools, are adding, each in its special field, to the combined total of medical research

Henrotin Hospital

done in Chicago. Among them are the Hektoen Institute, the McCormick Institute for Infectious Diseases, now part of Cook County Hospital, and the Institute of Psychoanalysis. The Chicago Institute of Medicine sponsors annually a series of lectures which draws medical men from distant points.

This brief review of the outstanding institutions of medical education and research is incomplete. It is hoped, however, that it will serve as a quick "tour." Every institution and group will welcome you during your stay here. Perhaps you, too, will leave feeling that Chicago is on the way to becoming the medical capital of the world.

Note: The kindness of the *Chicago Daily News*, in granting permission to use in this account certain information contained in articles by Arthur Snider which it published, is gratefully acknowledged. The source of many of the statements concerning Chicago's past medical accomplishments is the "History of Medicine and Surgery and Physicians and Surgeons of Chicago," endorsed and published under the supervision of the Council of the Chicago Medical Society by the Biographical Publishing Corporation, Chicago, Illinois, 1922.